Organic synthesis using new approaches to asymmetric catalysis

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Award date:
2002

Awarding institution:
University of Bath

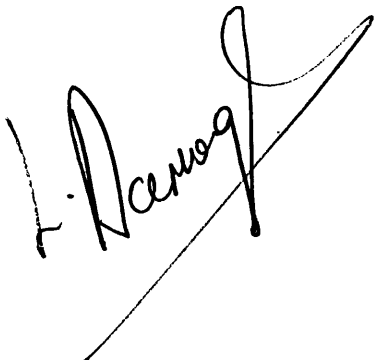
Organic Synthesis Using New Approaches to Asymmetric Catalysis

submitted by Lara Acemoglu

for the degree of PhD

of the University of Bath

January 2002



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Abstract

This thesis is concerned with regio- and enantiocontrol in the palladium catalysed allylic substitution reaction.

Two reviews are covered in chapter 1, describing the reaction mechanism and synthetic scope in the palladium catalysed allylic substitution and reviewing some of the literature to date on palladium catalysed asymmetric allylic allylation reactions.

The second chapter is concerned with the enantioselective synthesis of 2-arylpropanoic acids such as Ibuprofen and Naproxen, whereby asymmetry is introduced into the molecule by using a palladium catalysed asymmetric allylic substitution strategy as the key step of the synthesis.

Regioselectivity of nucleophilic attack, in the Pd/ Cy_3P catalysed reaction of monosubstituted allylic substrates is investigated in chapter 3. We have demonstrated that the branched acetate **263** undergoes palladium-catalysed allylic substitution with $NaCH(CO_2Me)_2$ to provide the branched substitution product with up to 120:1 regiocontrol when dichloromethane is employed as the solvent. The origin of this effect as well as the synthetic scope of this reaction has been investigated.

Acknowledgements

I would firstly like to thank my supervisor, Prof. Jonathan Williams, for all his valuable help and encouragement throughout my PhD. I feel extremely privileged to have had the opportunity to work with Jon. He truly has all my admiration both as a supervisor and as a friend. Thank you Jon!

I have also had the pleasure of working alongside Phi, Matt Clarke, Louse T., Amin, Gian, Mark, Parminder, Kerry, Christian, Becky, Alison, Steve, Tim, J-P, Phill and Claudia from Jon's research group. Thanks also go to other members of the chemistry department.

I would also like to thank Alan, John, Russell, Harry, Dave and Chris for their technical assistance.

A loving thank you goes to my fiancé, Steven Durrant, for always being there for me and for being great company in the lab.

Finally I would like to thank my mum and dad for being the most wonderful parents in the world. I still remember the day I came to England for my education and the day my mother settled me at boarding school and waved me goodbye. It has not been easy to be away from my parents for so many years and I know that it has been hard for them too. They have sacrificed so much for my education and I could not thank them enough in words for all they have done for me. All of this would have been impossible if it was not for my mum and dad.

Dedicated to my Mum and Dad

Alice and Garo

Contents

Abbreviations

Ac	acetate
B-	branched
BINAP	2,2 *Bis*(diphenylphosphino)-1,1-binaphthalene
Boc	
BSA	N,O-*bis*(trimetylsilyl)acetamide
Bz	Benzyl
Carb	Carbonate
cat	catalyst
Cp	cyclopentadiene
Cy	cyclohexyl
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undecene-7
DCM	Dichloromethane
de	diastereomeric excess
DMAP	Dimethylaminopyridine
DMF	Dimethylformamide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMSO	dimethyl sulfoxide
dppe	1,2-bis(diphenylphosphinoethane
ee	enantiomeric excess
ent-	enantiomer
EtOAc	ethyl acetate
EtOH	ethanol
GC	gas chromatography

h	hour
HPLC	High Performance Liquid Chromatography
Hz	Hertz
IPA	isopropanol
IR	Infra Red
L-	linear
Ln	ligand
MeOH	methanol
MeO-MOP	2-diphenylphosphino-2-methoxy-1,1-binaphthyl
NMR	Nuclear Magnetic Resonance
Nuc	nucleophile
PDC	pyridinium dichromate
Piv	pivalate
rt	room temperature
THF	tetrahydrofuran
tlc	Thin layer chromatography
TM	transition metal
Ts	tosylate

Chapter 1

Reviews

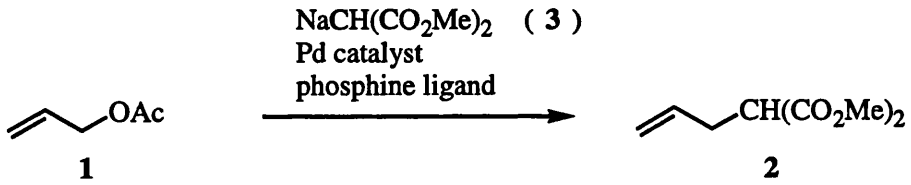
1 Reaction Mechanism and Synthetic Scope in the Palladium-Catalysed Allylic Substitution

A. Introduction

In 1965 Tsuji reported that a limited range of nucleophiles react with palladium allyl complexes, and in the early 1970's a catalytic variant was devised. Since that time the palladium catalysed allylic substitution reaction has become a crucial method for the formation of carbon-carbon and carbon-heteroatom bonds and it continues to be one of the most investigated areas in literature. Palladium catalysed allylic substitution reactions can cover a wide range of nucleophiles, leaving groups and substrates.[1],[2] The aim of this review is to present the reader with the historical development and to give an account of progress in literature since 1997.

The prototype reaction is provided by the conversion of allyl acetate **1** into the substitution product **2**.[3] In this case, the nucleophile **3** is an enolate derived from malonate, and provides a typical example of a stabilised nucleophile (**Scheme 1**).

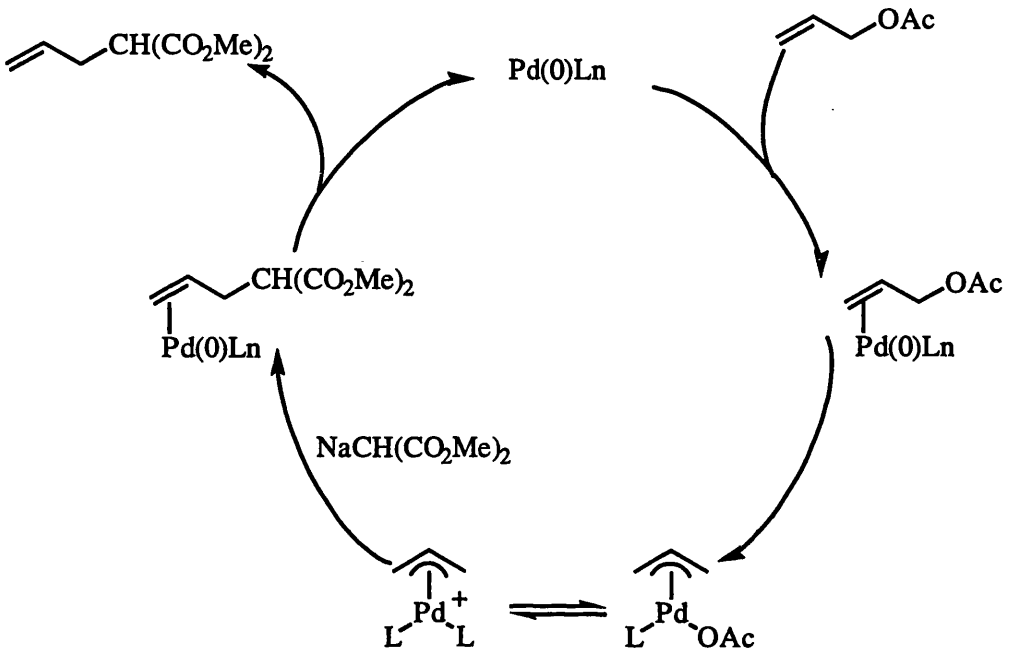
Scheme 1



The generally accepted mechanism for palladium catalysed allylic substitution is outlined below (**Scheme 2**). It is believed that the mechanism involves the initial co-ordination of Pd(0) to the alkene , followed by an oxidative addition process to afford an intermediate η^3-allyl complex. Nucleophilic addition to the cationic

complex is followed by a dissociation process which results in liberation of the product and regeneration of the active Pd catalyst.

Scheme 2

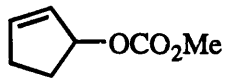


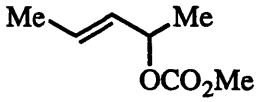
B. Range of leaving groups

Although several leaving groups have been shown to be effective, acetate and carbonate leaving groups are by far the most common.

Carbonates (**Scheme 3**) are known to be more reactive in comparison to acetates, hence an allylic substrate, which has both an acetate and a carbonate leaving group, reacts preferentially on the carbonate. One of the advantages of carbonates is that the allylation takes place in neutral medium as for example, an ethoxycarbonyloxy leaving group decomposes into CO_2 and ethoxide anion. This is basic enough to take a proton from certain pronucleophiles generating *in situ* the actual nucleophilic species (Nu^-).

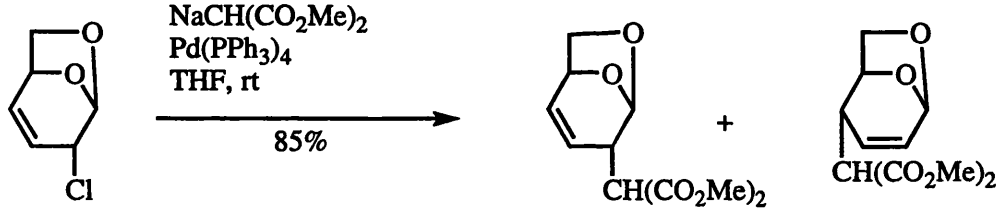
Scheme 3





Halides have been used as the leaving group on a few occasions.[4] For example, the chloride **4** has been reacted with a range of stabilised enolates including the anion of dimethylmalonate (**Scheme 4**).[5]

Scheme 4



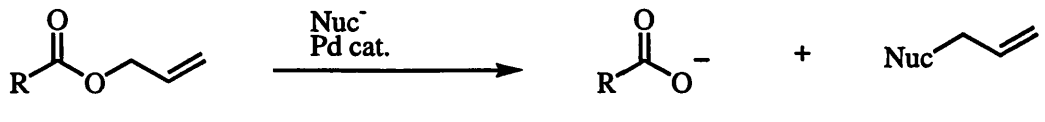
4 **5** **6**

(84:16)

Allylic alcohols are not generally used as substrates, as OH^- is not a good enough leaving group.[6] However, substitution on activated allylic alcohols has also been carried out on a number of occasions. [7],[8]

Carboxylates other than acetate can be used as the leaving group, including pivalate and benzoate.[9] Allyl groups can be used as protecting groups for carboxylates, since palladium catalysed allylic substitution can remove these groups (**Scheme 5**).[10],[11]

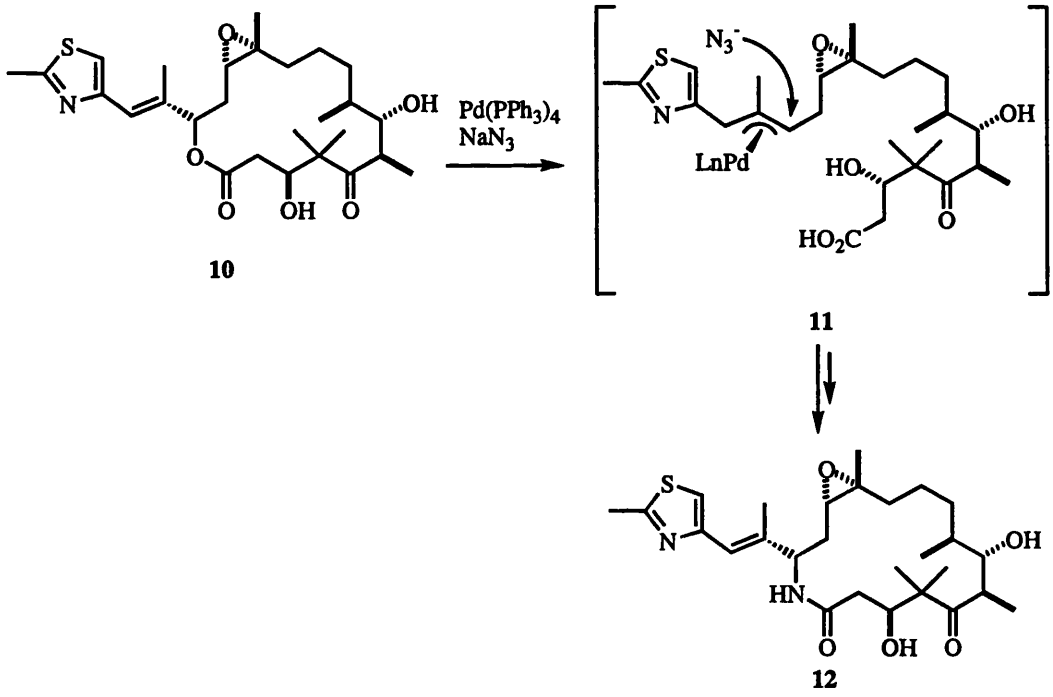
Scheme 5



7 **8** **9**

Unsaturated lactones are interesting substrates for palladium catalysed allylic substitution reactions.[12] Borzilleri[13] has used the ring opening reaction of lactone **10** to synthesise a range of biologically active lactams, including **12**. The π-allylpalladium complex **11** is trapped with a 'soft' external nucleophile such as azide. Subsequent reduction of the azide followed by macrocyclisation provides epothilone-lactams (**Scheme 6**). Relief of ring strain is believed to be the main driving force behind these reactions. Surprisingly all the potentially labile functionality found in the epothilone core, including the epoxide, remains intact. This illustrates one of the great advantages of palladium as a catalyst.

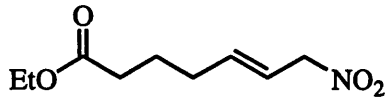
Scheme 6



10 **11** **12**

Allylic nitrates such as **13** and **14** have also been shown to undergo allylic substitution with various nucleophiles including $NaCH(CO_2Me)_2$ to give reasonably good yield of products.[14] (**Scheme 7**).

Scheme 7



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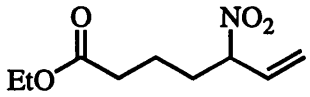


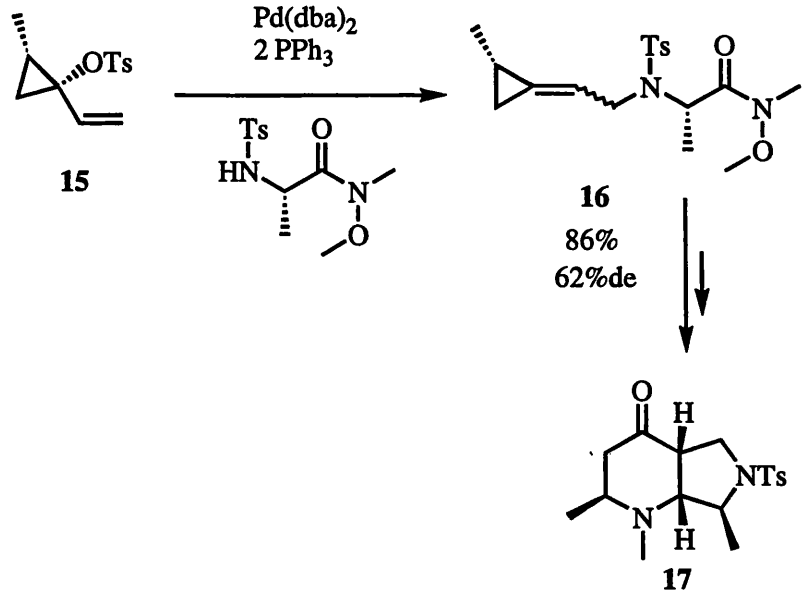
14

Vinylogous sulfonates,[15] phosphates[16] and carbamates[18] have been used as leaving groups. The vinylogous sulfonate group provides a more rapid reaction in comparison with acetates. Ethers have also been used as leaving groups,[19] and work best when either phenyl esters[20] or epoxides are employed.

The use of allyl acetates has been extended to incorporate related structures including allylic diacetates[20] and dienyl acetates.[21],[22]

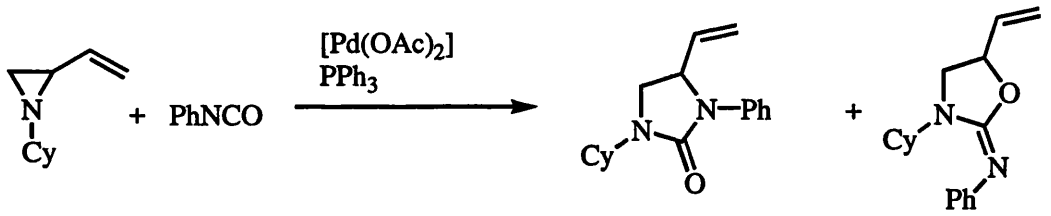
In spite of their inherent ring strain, alkylidenecyclopropanes are readily available compounds and form another interesting class of substrates for palladium catalysed allylic substitution reactions. For example, Brandi[23] has recently used these substrates for the synthesis of diazaheterocycles. Elaboration of the substituted product **16** afforded compound **17** in three steps (**Scheme 8**).

Scheme 8



Vinylaziridines with their nitrogen leaving group have also attracted some attention. For instance, Alper[24] has recently demonstrated that these substrates can be used in the ring-opening cyclisation reactions with isocyanates, carbodiimides and isothicyanates to afford five-membered heterocycles (**Scheme 9**). Interestingly this cycloaddition reaction takes place at room temperature. The driving force is believed to be the presence of an intermediate (π-allyl)metal complex. A mixture of structural isomers **19** and **20** is a consequence of N- and O-alkylation.

Scheme 9

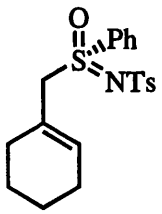


18 **19** **20**

19:**20** 2:1

Apart from oxygen and nitrogen nucleophiles sulfur leaving groups have also been used on some occasions. Examples include allylsulfoximines[26] **22** (**Scheme 10**).

Scheme 10



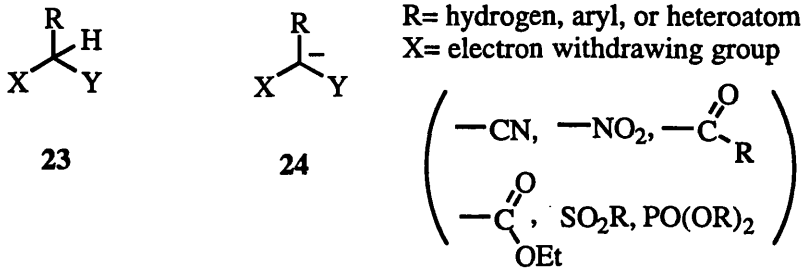
22

C. Range of stabilised carbon nucleophiles

The nucleophiles that can be considered as behaving in a similar way to stabilised enolates have the general structure **24**. In general, the anion (enolate) is preformed by addition of base, often sodium hydride, to the pronucleophile **23** (**Scheme 11**).

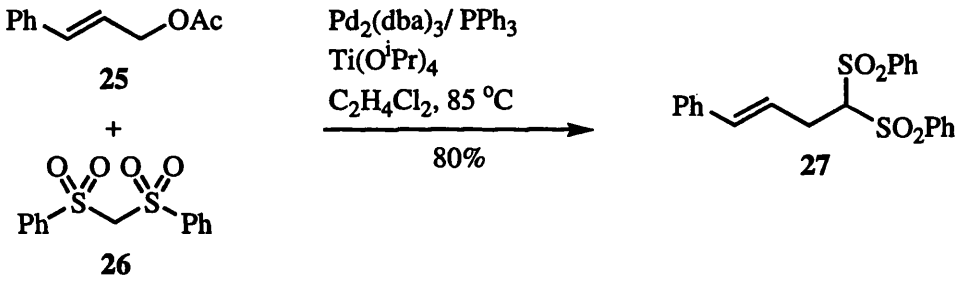
If the pKa of the pronucleophile is sufficiently low, then the acetate leaving group can act as an *in situ* base.[27]

Scheme 11



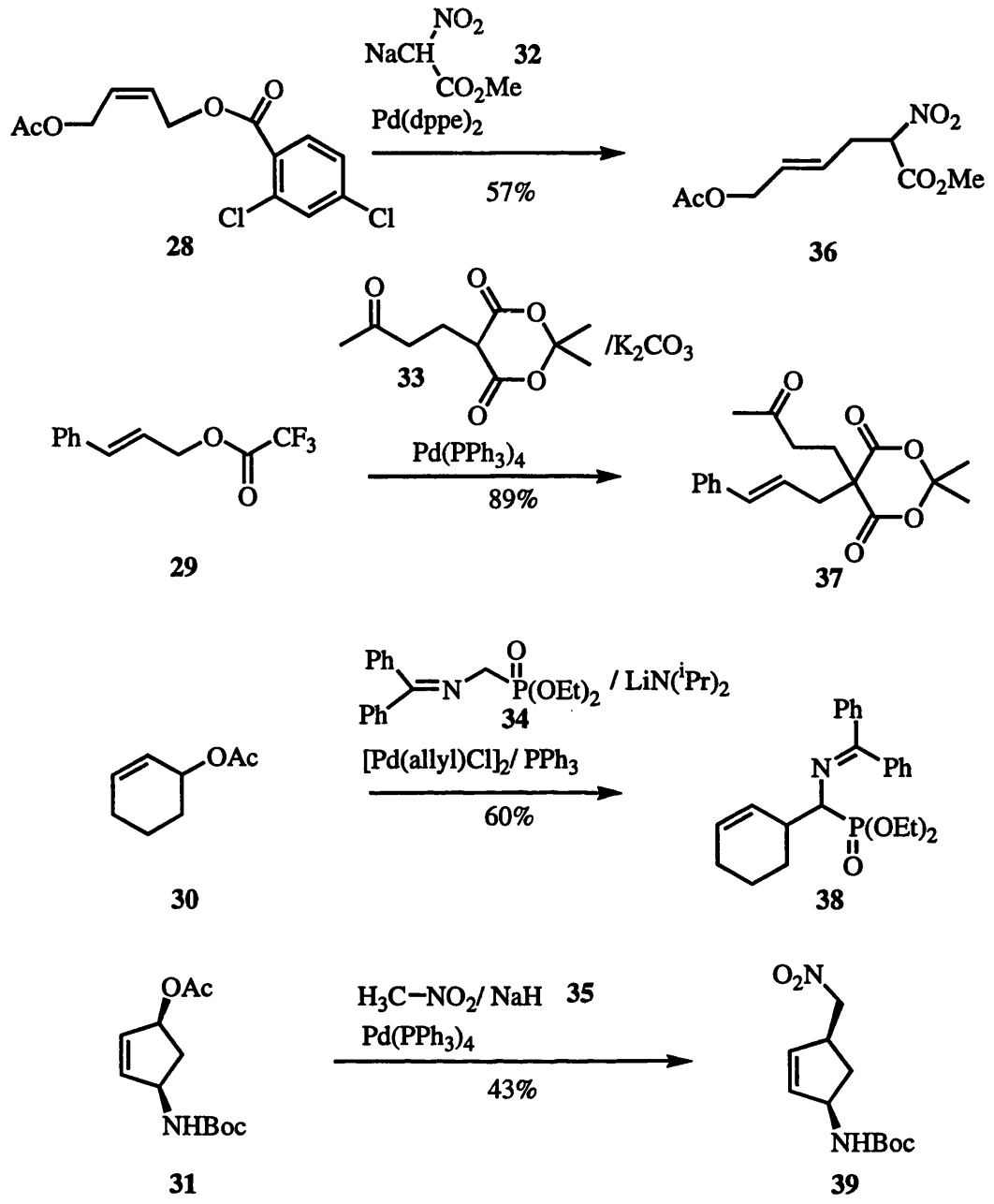
Titanium tetraisopropoxide has also been used to promote palladium-catalysed allylic alkylations, as exemplified by the reaction of cinnamyl acetate **25** with the bis-sulfone **26**[29] (**Scheme 12**).

Scheme 12



Further examples of stabilised carbon-centred nucleophiles used in palladium catalysed allylic substitution are given in **Scheme 13**.[30]-[37] It is noteworthy that the dichlorobenzoate group of substrate **28** leaves selectively over the acetate, and that the (*Z*)-stereochemistry of the substrate becomes (*E*)-stereochemistry in the product **36**. Nitromethane **35** is sufficiently acidic that there are no problems in the substitution reaction with acetate **31**. Relative stereochemistry is preserved in the product **39**.

Scheme 13



D. Stereochemistry of allylic substitution reactions

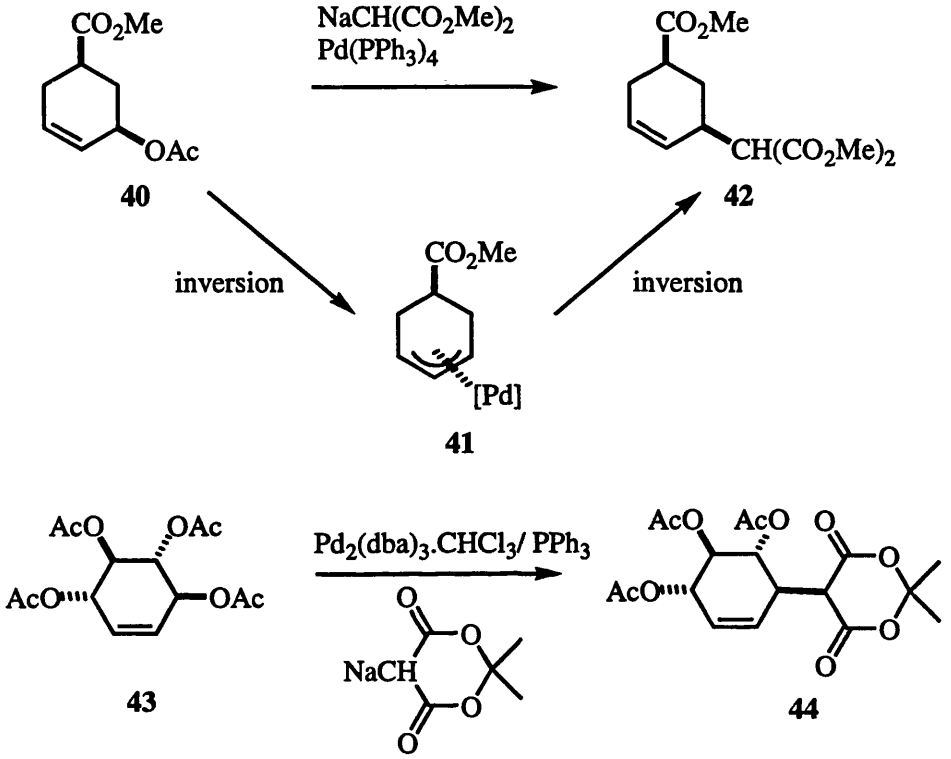
Soft nucleophiles react with overall retention of stereochemistry with suitable substrates (**Scheme 14**). For example, the relative stereochemistry of cyclohexenyl acetate **40** is retained upon reaction with stabilised enolates.[38]

The mechanism proceeds *via* a double inversion. The palladium displaces the acetate with inversion to give complex **41** and the incoming nucleophile

approaches from the opposite face to the palladium, again with inversion. Therefore, overall retention of stereochemistry is observed in the product **42**.

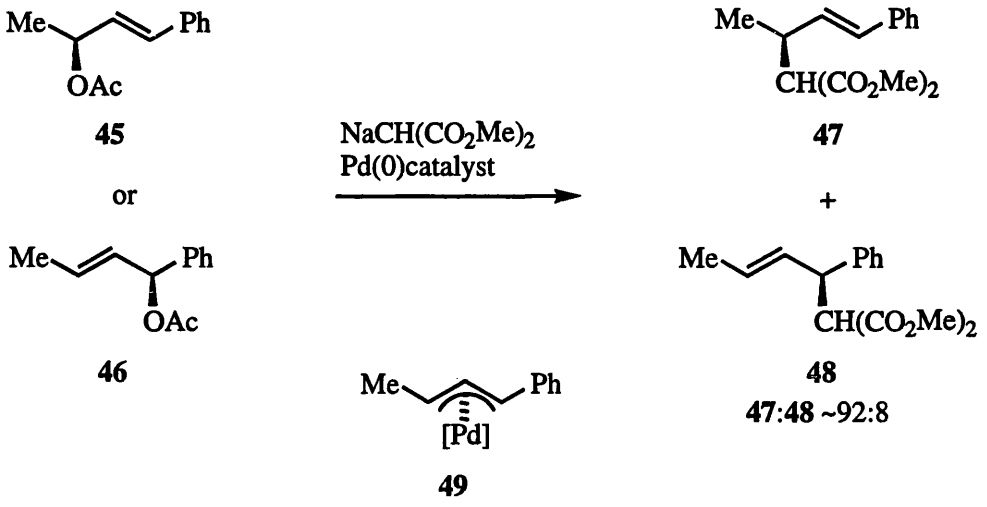
An example indicating the retention mechanism in cyclic substrates is provided by the reactions of substrate **43**,[40] that leads to the formation of compound **44**.

Scheme 14



There have also been examples of retention of stereochemistry in acyclic substrates (**Scheme 15**). The enantiomerically pure acetates **45** and **46** undergo palladium catalysed allylic substitution with retention of stereochemistry.[41] The regioisomeric ratio of products **47** and **48** is almost identical, indicating that the reaction proceeds *via* the common intermediate **49**.

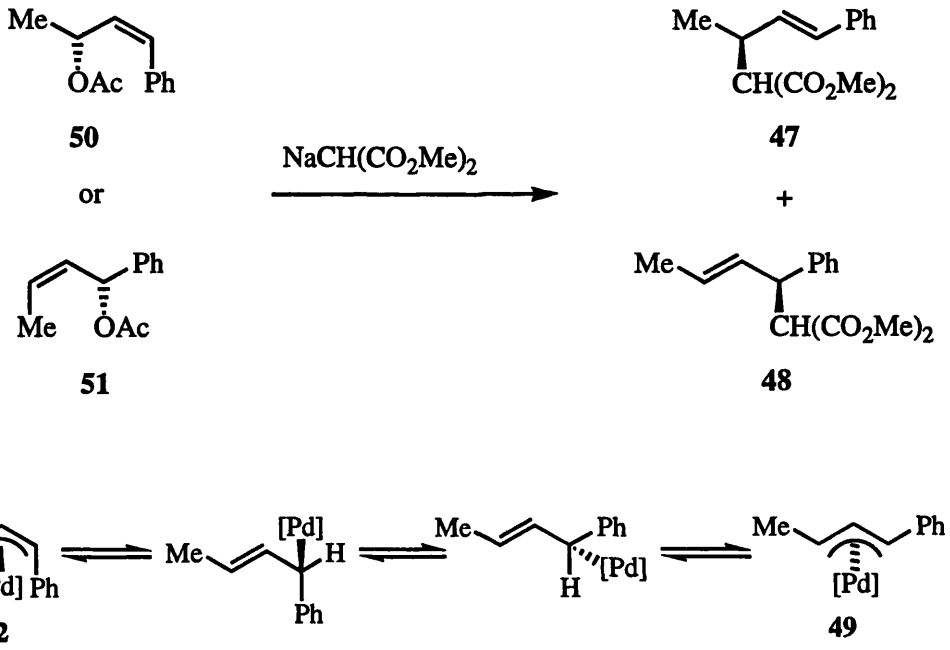
Scheme 15



Interestingly, the same enantiomers of products **47** and **48** are formed starting from the other isomer of the (*Z*)-allyl acetates **50** and **51** (**Scheme 16**).

It is reasoned that the initially formed π-complex **52** undergoes π-σ-π rearrangement to give the common intermediate **49** prior to attack of the nucleophile.

Scheme 16

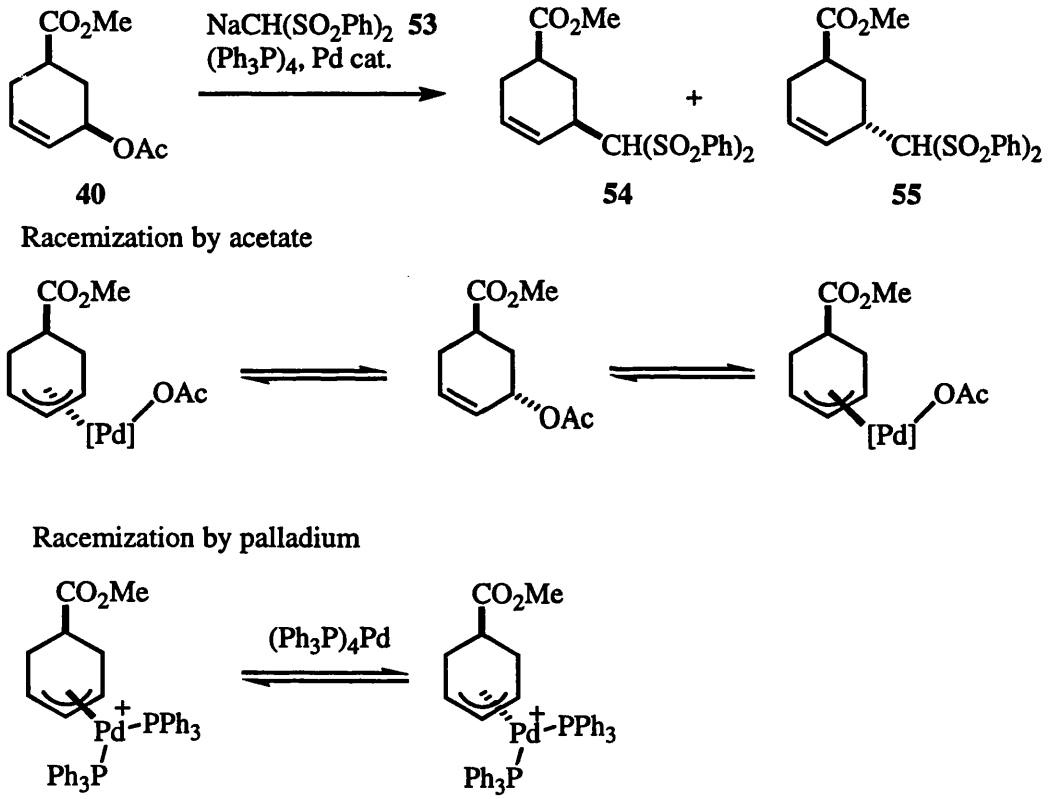


In fact, the stereochemical integrity of allyl acetates is not always faithfully preserved in the reaction to give the substitution products. It is known that acetate

can scramble the stereochemistry of allylpalladium complexes. The mechanism probably involves delivery of acetate from the palladium to the allyl moiety. In cases where the nucleophile attacks slowly, an erosion of stereochemical integrity will be seen.

For example, the bulky nucleophile **53** reacts slowly with the intermediate allylpalladium complex, which allows time for inversion to take place as indicated in **Scheme 17**.[42]

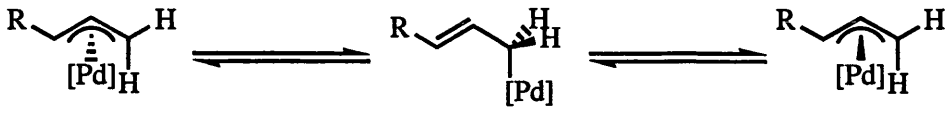
Scheme 17



The racemisation or epimerisation of allylpalladium complexes can also be caused by additional palladium(0).[43] The palladium exchange is particularly problematic when high concentrations of catalyst are employed.

Allylpalladium complexes are also able to undergo racemisation *via* a π-σ-π mechanism. This occurs rapidly when one terminus of the allyl group contains identical substituents, often hydrogen. Temporary formation of a σ-complex affords an achiral species, which can revert to either enantiomer of π-complex **(Scheme 18)**.

Scheme 18



Thus, whilst the well known double-inversion mechanism can provide a route for the conversion of enantiomerically pure substrate into enantiomerically pure product, this may not always be observed.

E. Solid phase catalysis

The use of catalysts that are supported on a solid phase is becoming increasingly popular. Such procedures allow for catalyst recycling and also reduce the levels of palladium/phosphine contamination in the final product. The polyethylene bound palladium complexes[6],[45] as well as malonate nucleophile attached to polymer[46] have been used successfully in allylic substitution reactions.

In summary, the palladium catalysed allylic substitution reaction between allyl acetates (and related electrophiles) with "soft" enolates has a wide scope and continues to attract considerable interest as a synthetic tool.

2 Palladium-Catalysed Asymmetric Allylation Reactions

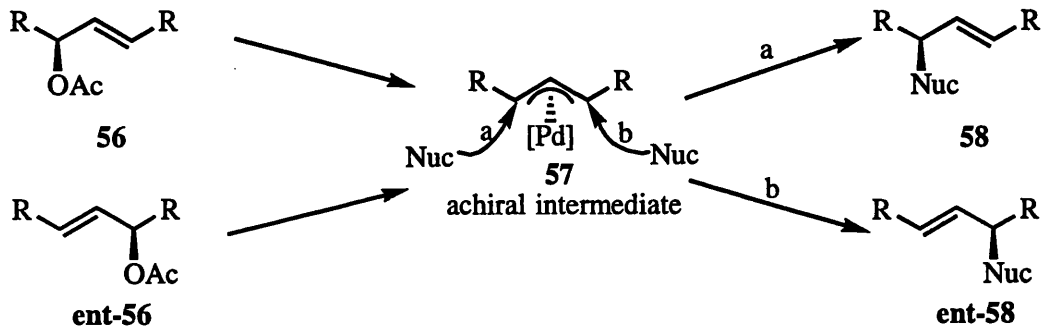
A. Introduction

Asymmetric variants of the palladium-catalysed allylic substitution reaction have enjoyed considerable attention since the first stoichiometric example reported in 1973.[47] The reaction has been the subject of several reviews,[48]-[51] and in some cases, the levels of enantioselectivity have reached in excess of 99% ee.

B. Reactions of 1,3-diphenylpropenyl acetate

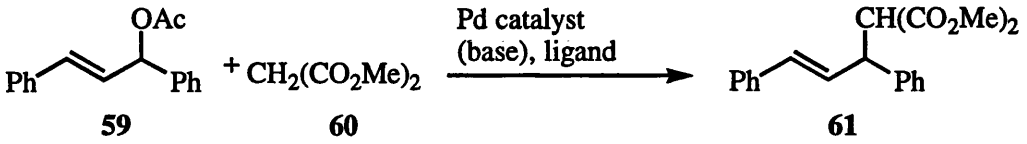
Allyl acetates **56/ent-56** that possess identical R groups undergo allylic substitution *via* an achiral intermediate **57**. Both enantiomers of starting material proceed *via* the same intermediate. In the absence of any controlling influence, approach of the nucleophile *via* pathways 'a' and 'b' is equally likely, and a racemic product **58/ent-58** will be formed (**Scheme 19**). However, the opportunity for an asymmetric catalytic reaction exists if the reaction can be channelled through one pathway selectively. Overall the process represents a dynamic resolution, since a racemic starting material is converted into an enantiomerically enriched product.

Scheme 19



Well over one hundred papers have been published describing the reaction of the particular substrate **59** reacting with dimethylmalonate **60** to afford the substitution product **61**. This reaction serves as a test-bed for newly designed ligands (**Scheme 20**).

Scheme 20

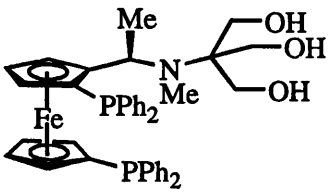


59 **60** **61**

One of the first design principles to address the asymmetric variant of this reaction considered ligands which were able to reach around the allyl moiety and direct the incoming nucleophile to one of the allyl termini selectively. Hayashi and co-workers developed ligands, **62** and **63**, which are able to influence the approach of the incoming nucleophile (**Scheme 21**).[52],[53],[54] Thus, with the standard allyl acetate substrate **59**, ligands **62** and **63** provide high levels of enantioselectivity in the substitution reaction with various stabilised enolates, including the enolate of pentane-2,4-dione, affording the substitution product **64** (**Scheme 21**).

Similar ligands involving a diphosphine ligand on a ferrocene framework with various functionalised pendant groups have been designed. Additionally, other ligands have been prepared with a similar strategy in mind, including ligands **65**,[55],[56] and **66**.[57],[58] In the case of ligand **65**, up to 99% ee was obtained in the conversion of pivalate ester **67** into the malonate-substituted product **61** (**Scheme 22**).

Scheme 21



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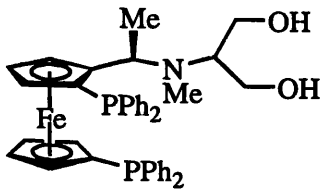
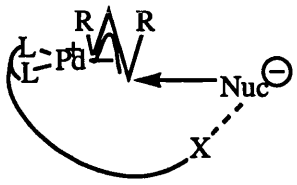
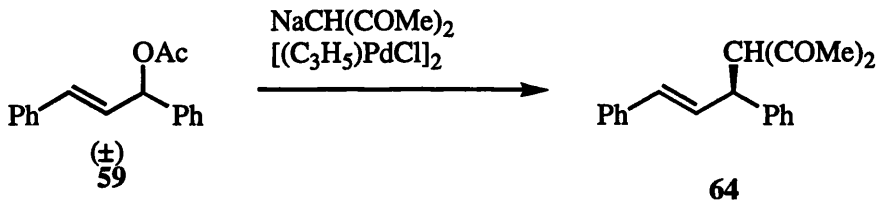


63

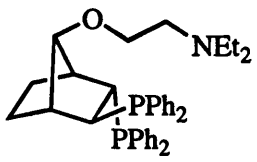




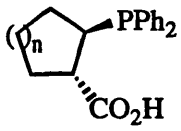
(±)
59

64

Scheme 22

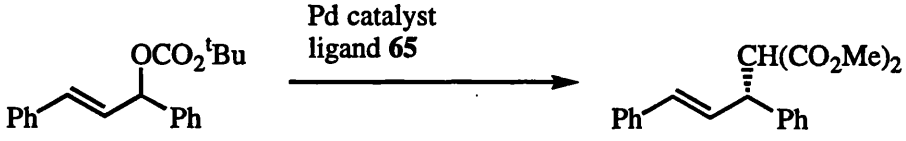


65



n=0, 1

66



67

61

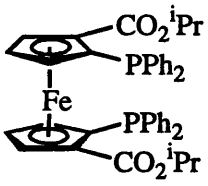
99% e.e.

The initial concept of an additional functional group providing guidance to the incoming nucleophile gave the first highly enantioselective examples of allylic substitution. However, the majority of ligands have not adopted this approach. The steric effect of a ligand on the allyl group can distort the symmetry of the allyl such that one end is further away from the palladium. It seems that the more

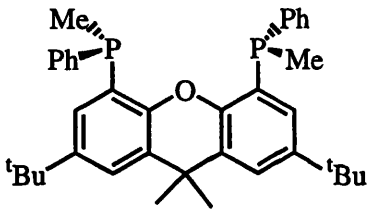
remote allylic terminus is generally the one which is attacked preferentially. It has also been proposed that a ligand can impart a 'twist' to the allyl group, which encourages attack at the allyl terminus which results in further rotation in the same direction.

Many bidentate ligands that contain identical donor atoms appear to induce asymmetry according to those ideas, especially when the ligands are C_2 symmetric. Examples of successful diphosphine ligands include the C_2-symmetric ligands **68-74** shown in **Scheme 23**. The quoted enantioselectivities refer to the preparation of the standard product **61**.

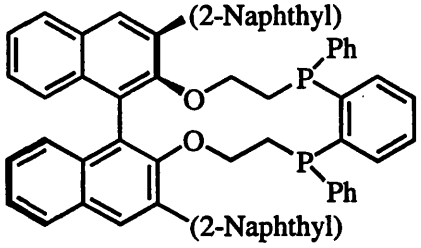
Scheme 23



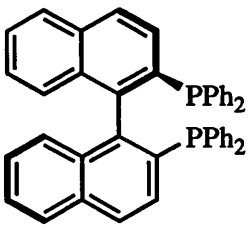
68[59],[60]
94% e.e.



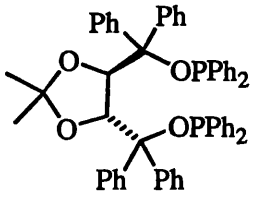
69[61]
85% e.e.



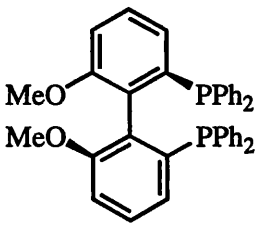
70[62]
98% e.e.



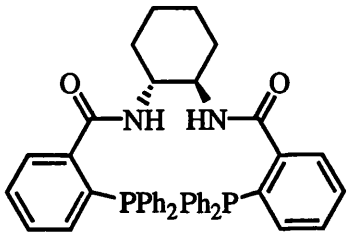
71[63],[64]
95% e.e. using acetamidomalonate
90% e.e. using microwaves



72[65]
70% e.e.



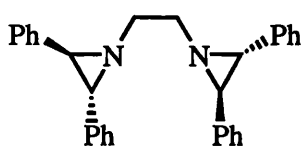
73[66]
95% e.e.



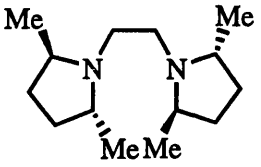
74[67]
(high ee's for suitable substrates)

The palladium catalysed allylic substitution reaction has been one research area where non-phosphorus based ligands have been actively investigated. There are many successful ligands containing two donor nitrogen atoms including those identified in **Scheme 24**. These ligands are either C_2-symmetric or nearly so.

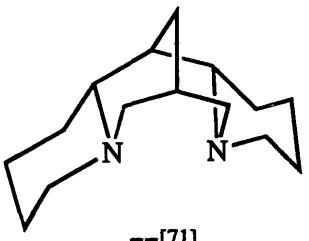
Scheme 24



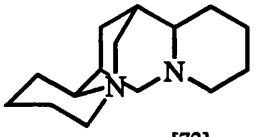
75[68],[69]
>99% e.e.



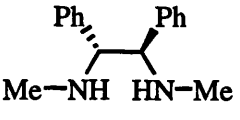
76[70]
91% e.e.



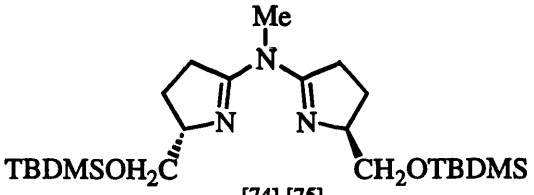
77[71]
95% e.e.



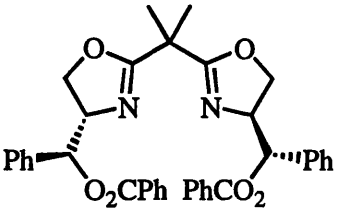
78[72]
85% e.e.



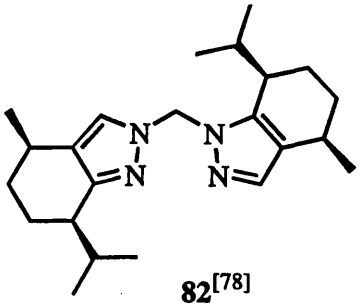
79[73]
95% e.e.



80[74],[75]
95% e.e.



81[76],[77]
90% e.e.

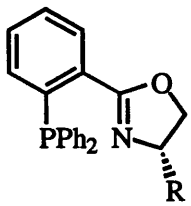


82[78]
84% e.e.

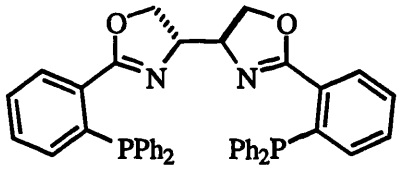
A further model for asymmetric induction in palladium catalysed allylic substitution reactions has been to employ ligands that contain two electronically different donor atoms. This approach is typified by the use of P,N ligands, where generally the phosphorus is considered to be a better π-acceptor than the nitrogen.

The idea that P,N ligands could perturb the symmetry of allylpalladium complexes had been established before the application to enantioselective catalytic systems.[79] The π-acceptor group has the effect of weakening and lengthening the Pd-C bond trans to itself (the trans influence). The incoming nucleophile is then better able to attack the compromised terminus of the allyl group. The asymmetric environment generated by the P,N ligand will lead to a preferred orientation (up or down) of the allyl ligand, and hence to an enantioselective process (**Scheme 25**).

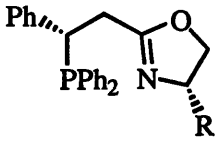
Scheme 25



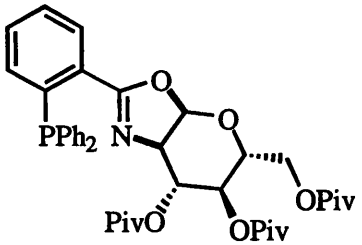
83[80]-[85]
(up to 99% e.e.)



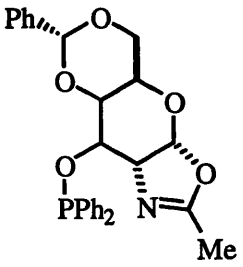
84[86]
97% e.e.



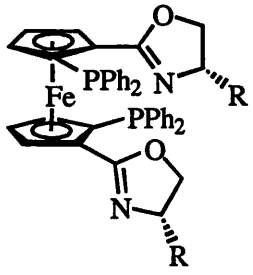
85[87]
98% e.e.



86[88]
98% e.e.



87[89],[90]
96% e.e.



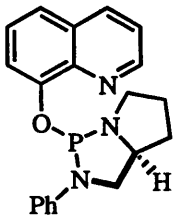
88[91]
99% e.e.

There have been many examples of successful P,N ligands, including the use of phosphines tethered to enantiomerically pure oxazoline groups. The originally reported ligands **83**[80]-[85] have been elaborated into a host of related structures.

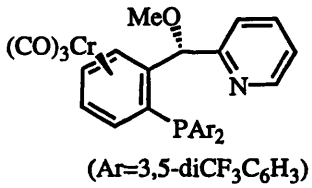
Ligand **85**[86]-[91] was identified as an effective ligand after screening a range of similar structures in a ligand library.[89]

Although the combination of a diphenylphosphino-group with an oxazoline has been very effective, especially for reactions of 1,3-diphenylpropenyl acetate **59**, other P,N combinations have also been popular.[92]-[97] The nitrogen donor can belong to a C=N unit, as shown in **Scheme 26**. Alternatively, various successful P,N-ligands have been reported that do not contain the nitrogen atom within a C=N bond. Some of those structures are identified in **Scheme 27**.[98]-[100]

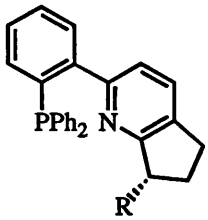
Scheme 26



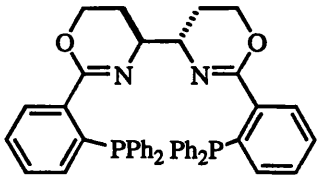
89[92]
85% e.e.



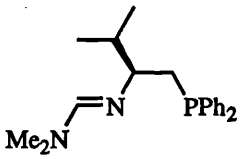
(Ar=3,5-diCF$_3$C$_6$H$_3$)
90[93]
93% e.e.



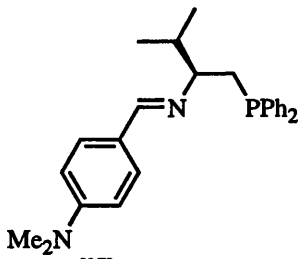
91[94]
98% e.e.



92[95]
84% e.e.



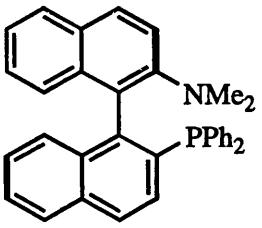
93[96]
95% e.e.
(with pivalate leaving group)



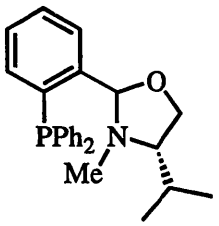
94[97]
92% e.e.
(with pivalate leaving group)

Whilst most good examples of heterobidentate ligands have been P,N ligands, there have been many other combinations of donor atoms, especially S,N ligands, some of which are clearly related to their P,N counterparts. **Scheme 38** shows some successful S,N ligands.[101]-[106]

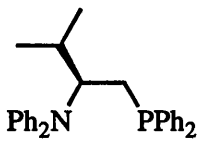
Scheme 27



95[98]
71% e.e.

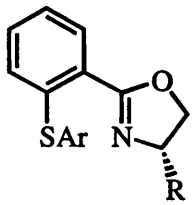


96[99]
98% e.e.

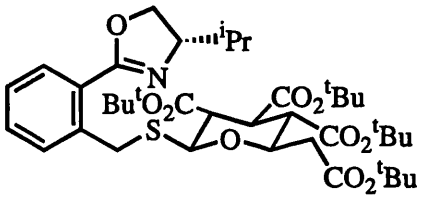


97[100]
92% e.e.

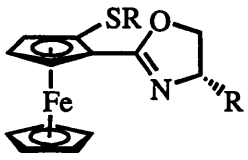
Scheme 28



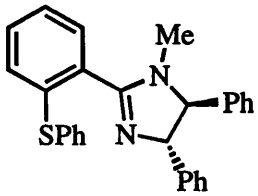
98[101]
99% e.e.



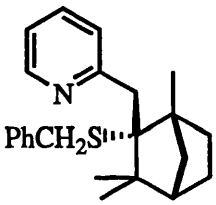
99[102]
97% e.e.



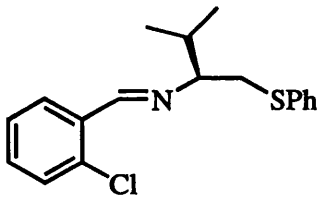
100[103]
98% e.e.



101[104]
96% e.e.



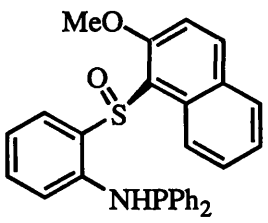
102[105]
98% e.e.



103[106]
94% e.e.

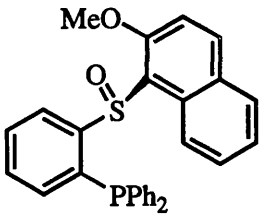
There have also been several reports of P,S ligands that have been employed to give high enantioselectivity in the palladium catalysed allylic substitution reaction of 1,3-diphenylpropenyl acetate **59** with malonate. Some of these ligands are identified in **Scheme 29**.[107]-[110]

Scheme 29



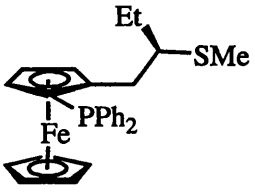
104[107]

97% e.e.



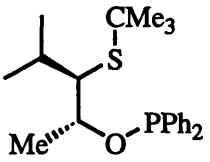
105[108]

82% e.e



106[109]

97% e.e.

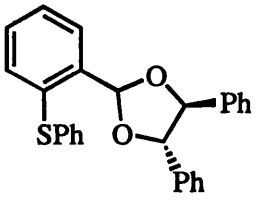


107[110]

98% e.e.

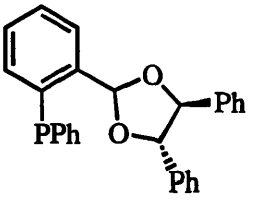
There have been a few reports of heterobidentate ligands containing oxygen donor ligands in combination with nitrogen, sulfur or phosphorus donor groups.[111]-[112] For example, cyclic acetals have been used, as represented by ligands **108, 109** and **110** in **Scheme 30.**

Scheme 30



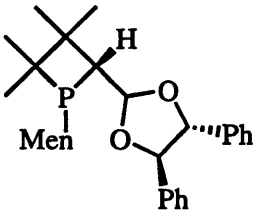
108[111]

82% e.e.



109[111]

88% e.e.



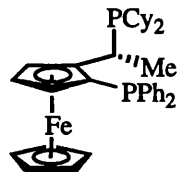
110[112]

91% e.e.

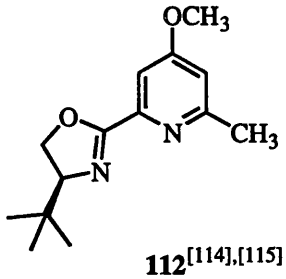
Men= menthyl

Even bidentate ligands that rely on donor atoms of the same element can still impart an electronic asymmetry on to the allylpalladium moiety. This can be achieved by changing the environment of the donor atoms relative to one another. A clear-cut example of this approach is seen in the case of ligand **111**, where the two phosphorus donor atoms are electronically quite distinct from each other.[113] There have also been many examples of non-C_2-symmetric dinitrogen ligands reported.[114]-[117] Their success may be attributed either to steric effects or, in some cases, an electronic difference between the two nitrogen donor atoms **(Scheme 31).**

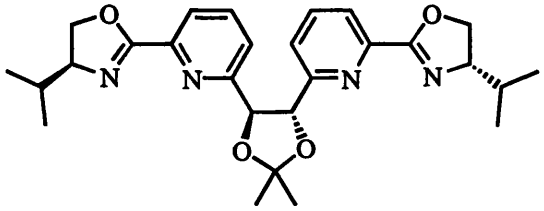
Scheme 31



111[113]
93% e.e.



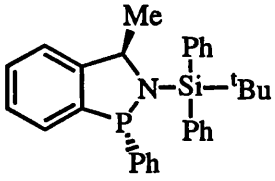
112[114],[115]
93% e.e.



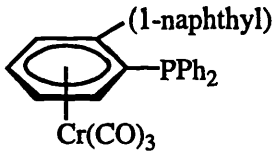
113[116],[117]
98% e.e.

Monodentate ligands form the last significant class of effective ligands for palladium catalysed allylic substitution reactions (**Scheme 32**). In principle, either one or two monodentate ligands could be associated to the allylpalladium complex. However, most successful monodentate ligands are bulky, suggesting that only one ligand is present.[118]-[120]

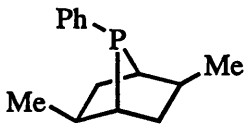
Scheme 32



114[118]
91.5% e.e.



115[119]
92% e.e.



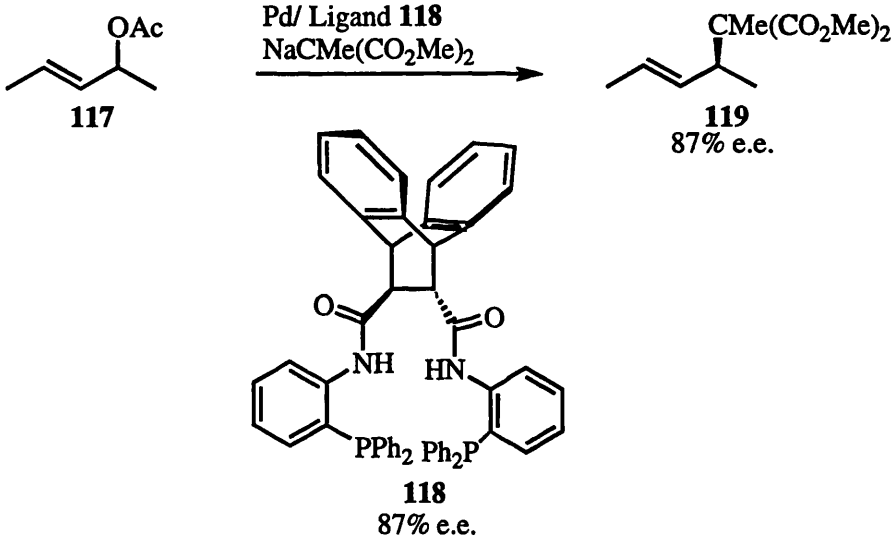
116[120]
97% e.e.

The ligands surveyed in the previous sections have been examined in the test-bed reaction, although this particular reaction conveys little about the success of the various ligands when other substrates are encountered, and it is helpful to consider the reactions of other substrates.

C. Other substrates

The allyl acetate **117** usually undergoes substitution reactions with lower enantioselectivity than the diphenyl counterpart **59** (**Scheme 33**). However, Trost's ligand **118** is able to induce up to 87% ee in the substitution product **119**.[121]-[122] The enantioselectivity achieved on the dimethyl substrate **117** was also improved upon modification of this ligand, whereby the phosphine units were designed to contain pendant arms able to associate with the nucleophile counterion.[123]

Scheme 33



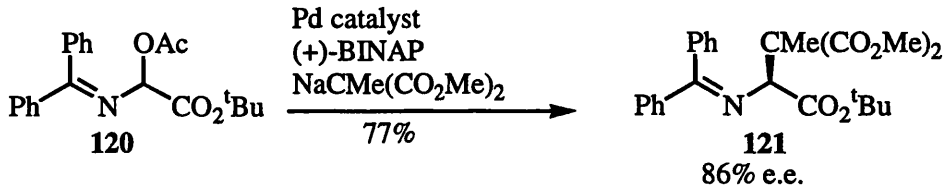
117

119
87% e.e.

118
87% e.e.

As well as the conventional all-carbon substrates, O'Donnell and co-workers have used the aza-analogue **120**.[124] (**Scheme 34**). This substrate proceeds *via* an intermediate π-allyl complex, although it is not a *meso*-system (see also substrate **132**).

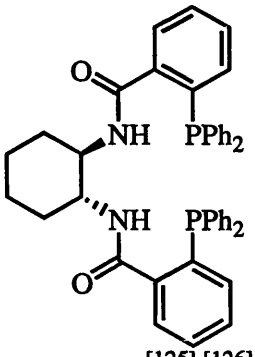
Scheme 34



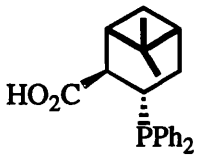
Cyclic substrates such as cyclohexenyl acetate **30** are also able to proceed *via* a *meso*-intermediate. The enantioselectivity of the reaction is determined by the selective approach of a nucleophile to one of the allylic termini of the intermediate.

Unfortunately, many of the ligands that give excellent selectivity in the substitution reactions of diphenylpropenyl acetate **59** give poor selectivity when cyclic acetates are used as the substrate. There are also many more cases where this information has not been reported. However, there are ligands that are capable of achieving excellent enantiocontrol for cyclic substrates (**Scheme 35**). Of particular note in this respect are the Trost ligands **74**.[125]-[126] The diphosphine ligands have a large 'bite angle,' which projects the chiral environment of the ligand more deeply into the area where the allyl group resides. Other ligands have also been shown to give high enantioselectivities for such cyclic allyl acetates.[110],[127]-[129]

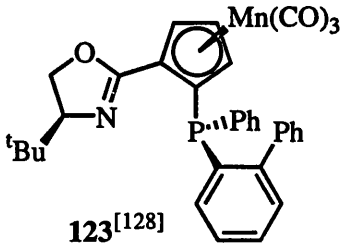
Scheme 35



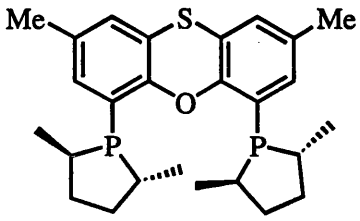
74[125],[126]



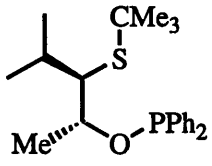
122[127]



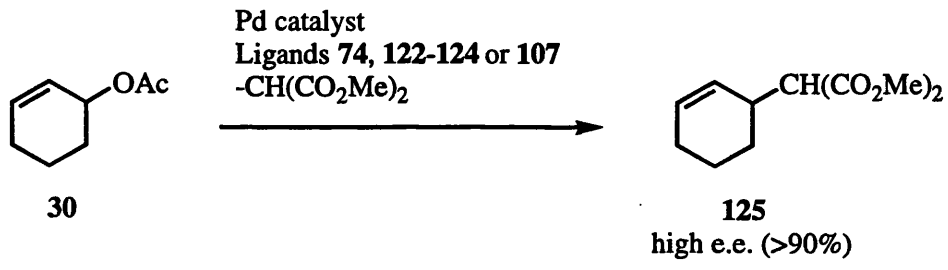
123[128]



124[129]

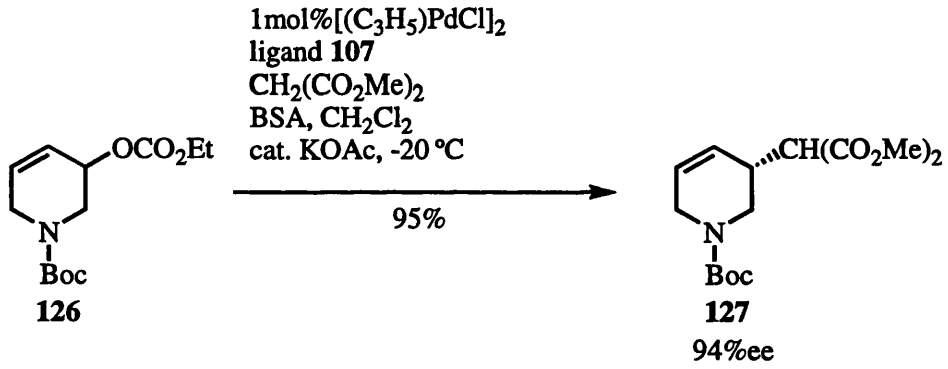


107[110]



30

125
high e.e. (>90%)



126

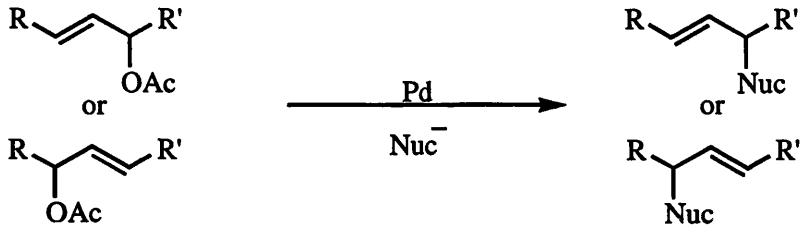
127
94%ee

D. Regiocontrol

The lack of regiocontrol in Pd catalysed allylic substitution is often a problem. In instances where the two termini of the allyl moiety possess non-identical groups, the issues of both regiocontrol and enantiocontrol can become important (**Scheme 36**). Typically, the nucleophile approaches from the less sterically hindered terminus, and the mechanism proceeds *via* a double inversion (overall retention)

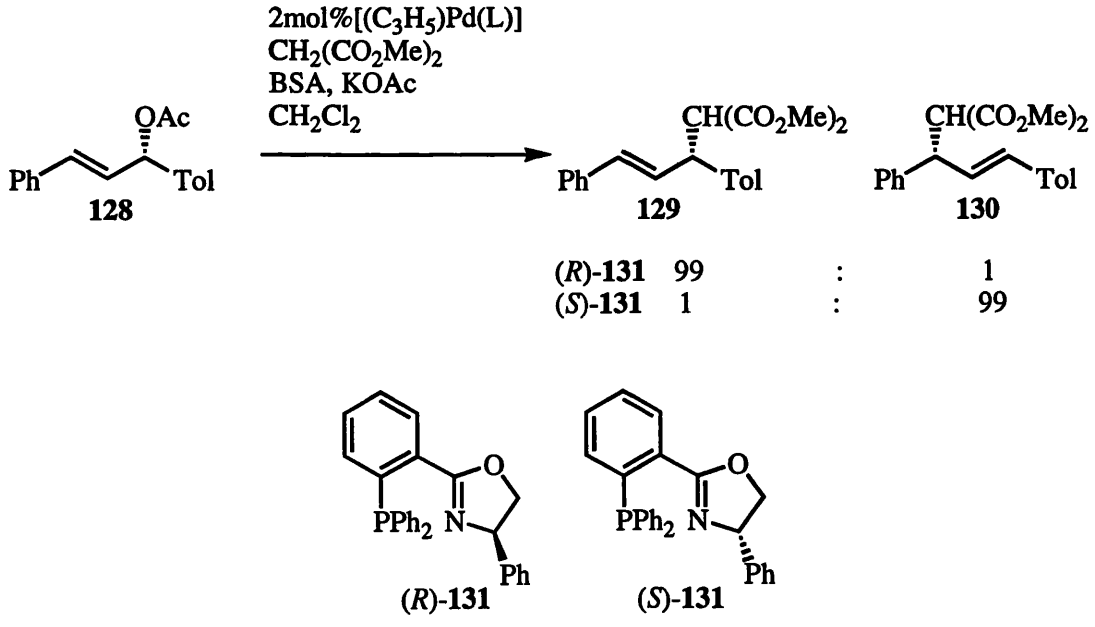
of stereochemistry process. Consequently, the use of a racemic substrate is unlikely to lead to a single regioisomeric product with high enantioselectivity.

Scheme 36



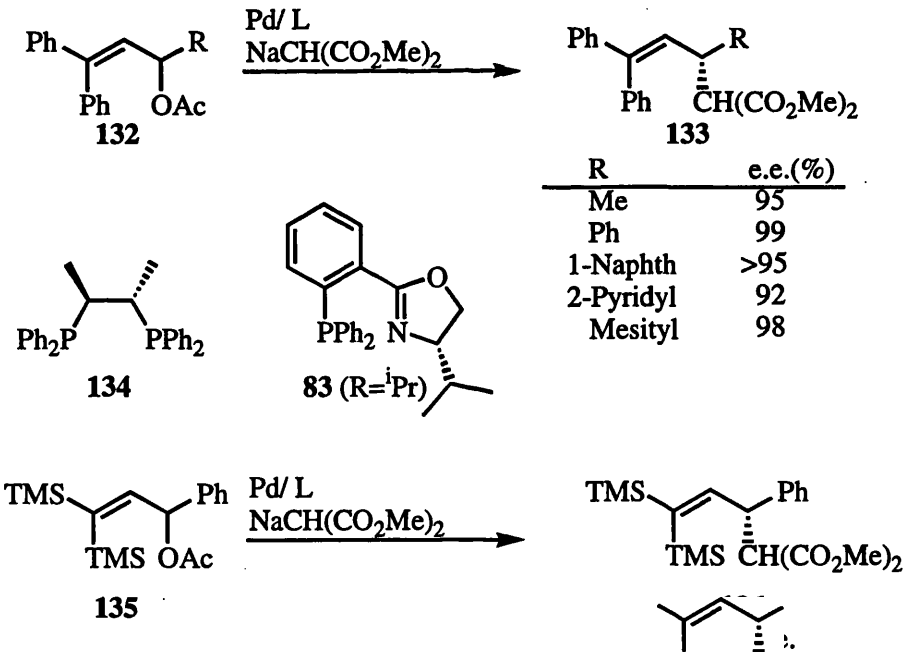
Pfaltz and co-workers have reported an interesting experiment using enantiomerically pure substrate **128**.[130] As expected, by the overall retention of stereochemistry mechanism, the nucleophile becomes attached to the substrate from the same face that the acetate had left from. However, by using the two enantiomers of ligand **131**, excellent control of regiochemistry could be established, affording either product **129** or **130** selectively (**Scheme 37**).

Scheme 37



Substrates with two phenyl groups at one end of the allyl group have been employed in enantioselective allylic substitution reactions. The regiochemical outcome is consistent with the majority of palladium catalysed allylic substitution reactions and the reaction has been extended to a range of R groups. Originally, substrates **132** were developed by Bosnich who employed chiraphos **134** as the ligand, affording up to 86% in the substitution product.[131] Sparteine **78**[72] has also been employed in the same reaction. However, phosphino-oxazoline ligands **83** have afforded particularly high enantioselectivities in these reactions (**Scheme 38**).[132] A similar strategy has been reported by Romero and Fritzen who used the disilylated substrate**135**. The silyl groups could be removed from the product **136** on treatment with acid.[133]

Scheme 38



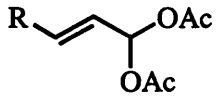
The issue of regioselectivity is dealt with in more detail in **Chapter 3.**

E. Replacement of an enantiotopic leaving group

Suitable diacetates are good substrates for enantioselective allylic substitution, when the selective replacement of one group will afford an enantiomerically enriched product. Typical substrates include *meso*-diacetates **137** and achiral diacetates **138** (**Scheme 39**).

Scheme 39

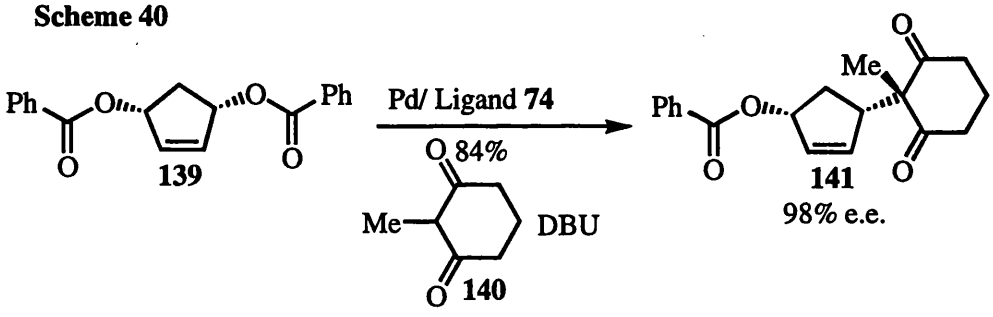
137
meso-diacetate



138
achiral diacetate

These substrates with enantiotopic leaving groups have received considerable attention from Trost's group, and much of the published work has come from this group.[134]-[137] Thus, ligand **74** has been used in the conversion of the *meso*-dibenzoate **139** into the mono-substituted product **141** with excellent enantioselectivity using the diketone **140** as nucleophile in the presence of base (**Scheme 40**).

Scheme 40

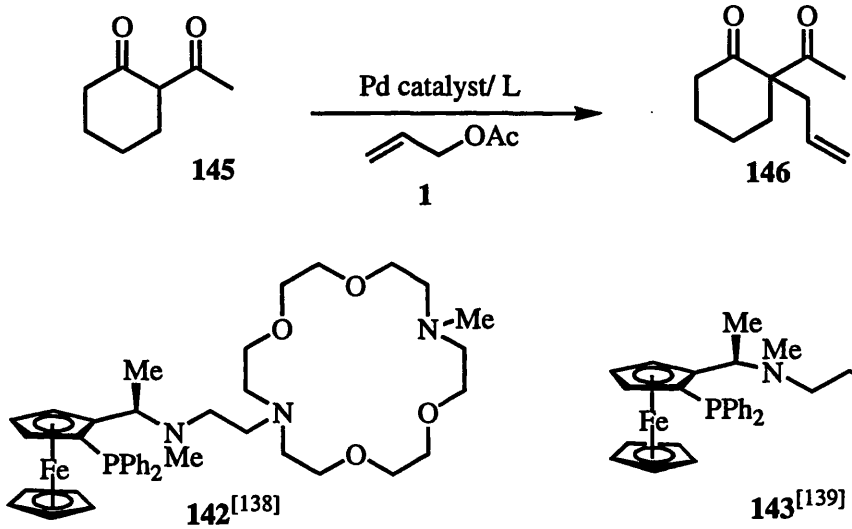


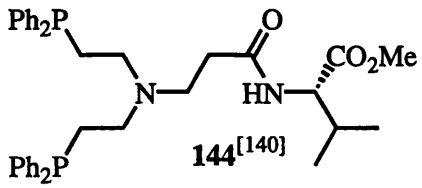
F. Prochiral nucleophiles

The use of a prochiral nucleophile in allylic substitution reactions provides an additional opportunity for asymmetric induction. Allyl acetate itself can be used as the electrophilic partner and the new sterogenic centre is positioned further away from the allyl group.

Ligands **142** to **144**, which are capable of binding to the palladium and also of steering the incoming nucleophile have been used in the allylation of the diketone **145 (Scheme 41).**[138]-[140]

Scheme 41



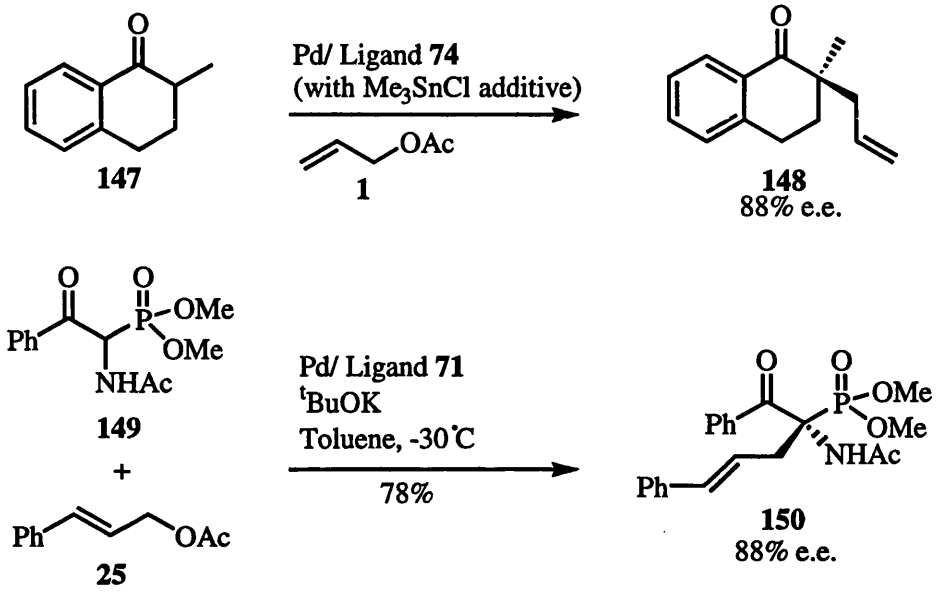


Ligand	e.e.(%)
142	75
143	81
144	52

Allylation of the ketone **147** was achieved, and although trimethyltin chloride was usually added, it was not an essential feature for obtaining reaction, once the ketone had been deprotonated with lithium diisopropylamide.[141]

Alkylation of cinnamyl acetate **25** using the β-ketophosphonate **149** has been carried out using a palladium/BINAP **71** catalyst (**Scheme 42**).[142]

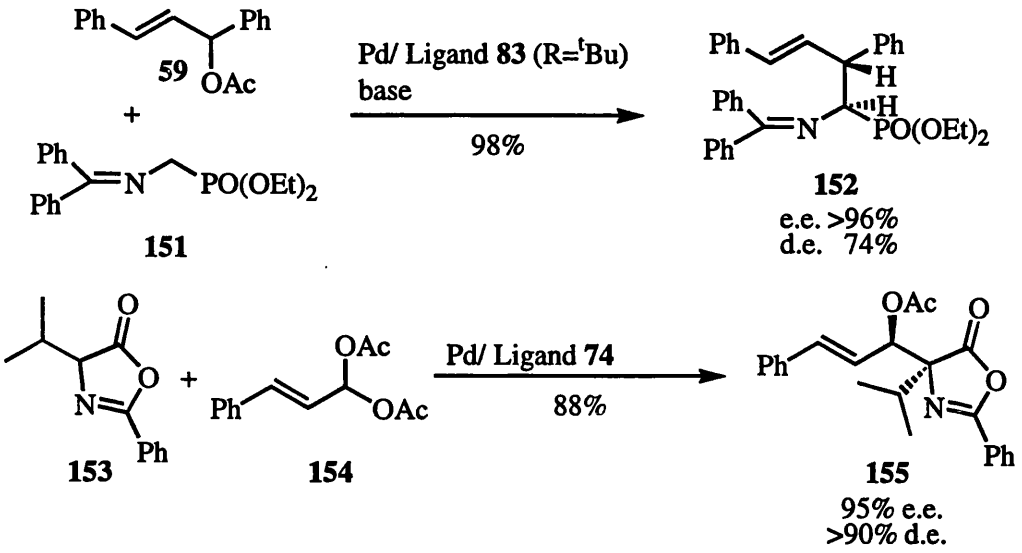
Scheme 42



When prochiral nucleophiles are employed with more complex allyl electrophiles, there is the possibility of forming two sterocentres in the product (**Scheme 43**). For example, imino phosphonate **151** has been used as the nucleophile in the reaction with allyl acetate **59**. The control of enantioselectivity at the benzylic position is very high, but there is lower relative stereocontrol at the newly formed stereocentre α- to the phosphonate group.[143]

The azalactone **153** has been used as a prochiral nucleophile in a similar process providing the substitution product **155** upon reaction with the gem-diacetate **154**.[144]

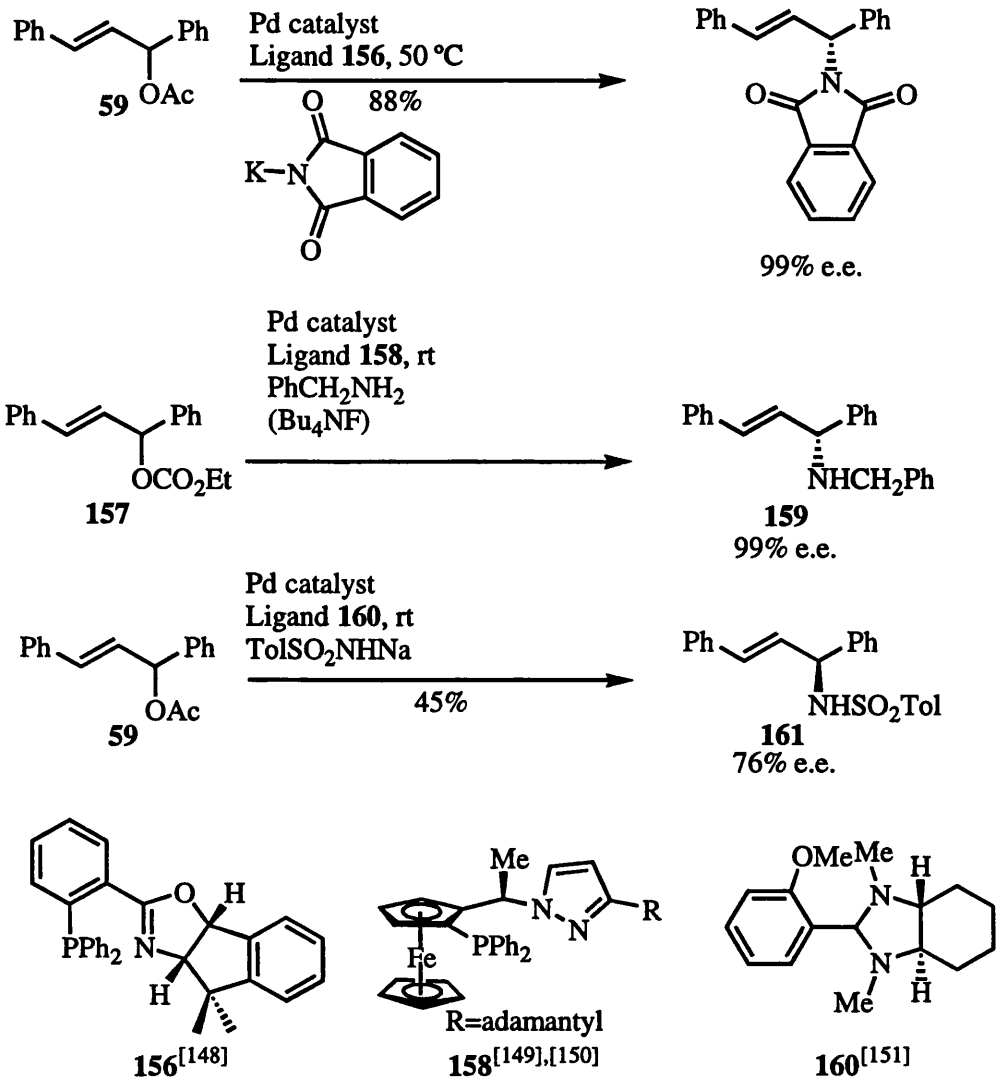
Scheme 43



G. Amination reactions

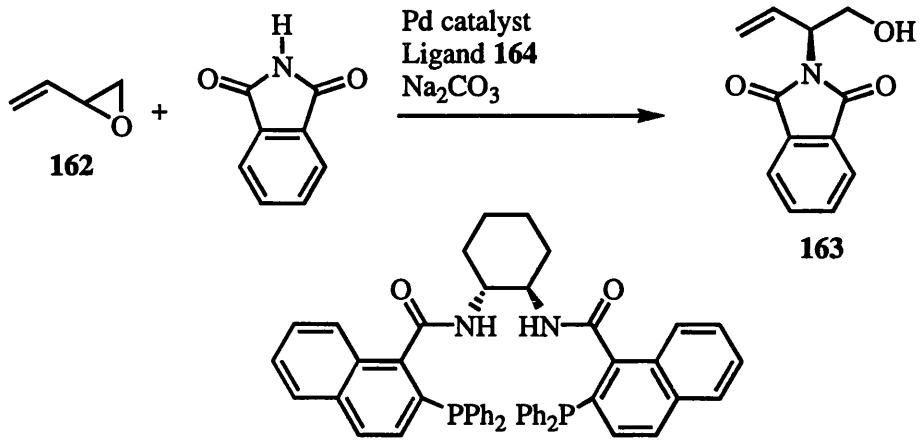
Apart from stabilised enolates, such as malonate anions, nitrogen nucleophiles represent the next largest class of nucleophiles to be used in enantioselective allylic substitution reactions.[145] Many of the best ligands for enantioselective allylic substitution with stabilised enolates are also, not surprisingly, good ligands for enantioselective allylic amination. There is therefore little point in identifying all of the successful allylic amination reactions, but a selection is offered in **Scheme 44**. For example, the test-bed substrate **59** has been shown by several groups to be amenable to enantioselective amination using phosphine-oxazoline ligands with sulfonamides, hydrazides, and benzylamine.[146]-[147] Sudo and Saigo have recommended phosphino-oxazoline **158** as a particularly competent ligand for allylic amination, and high enantioselectivities have been achieved using this ligand.[148] Other groups have used different ligands with carbonate substrates and other nitrogen nucleophiles, again achieving high enantioselectivity.[149]-[151]

Scheme 44



Butadiene monoepoxide **162** has been used as a substrate for enantioselective allylic substitution reactions. The reaction with phthalimide has been performed with excellent regiocontrol and excellent enantiocontrol. The best results were obtained with a variant **164** of the standard ligand (**Scheme 45**).[152]-[153]

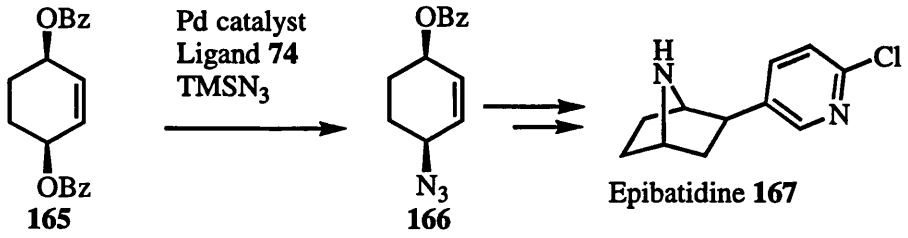
Scheme 45



162 163 164

Amination of substrates with enantiotopic leaving groups has been achieved (**Scheme 46**). Examples include the palladium catalysed azidation of the *meso*-dibenzoate **165**.[154] The product **166** was converted into epibatidine **167** by a series of transformations.[155]

Scheme 46



165 **166** Epibatidine **167**

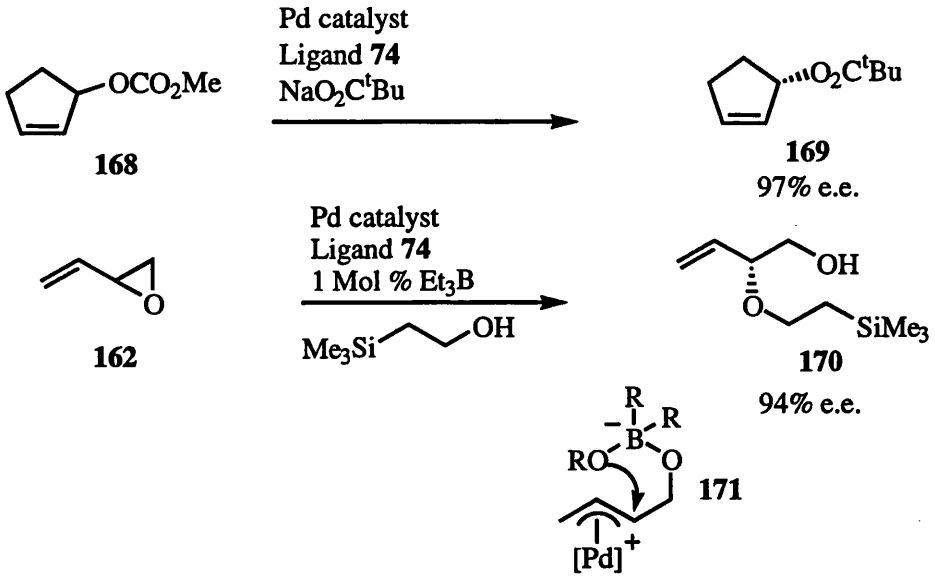
H. Other heteroatom nucleophiles

Whilst the majority of reports involve the use of carbon or nitrogen-based nucleophiles, sulfur, oxygen and even silicon[156] nucleophiles have also been recorded. In principle, oxygen nucleophiles have the potential to add reversibly to allylic systems. Complete reversibility of the reaction will afford racemic products, and hence efforts have been made to minimise reversibility (**Scheme**

47). For example, Trost and Organ have reported the reaction of racemic cyclopentenyl carbonate **168** with sodium pivalate to give enantiomerically enriched cyclopentenyl pivalate **169**.[157] Careful control of temperature was required in order for the product to remain inert under the reaction conditions, but for the more reactive carbonate to still participate.

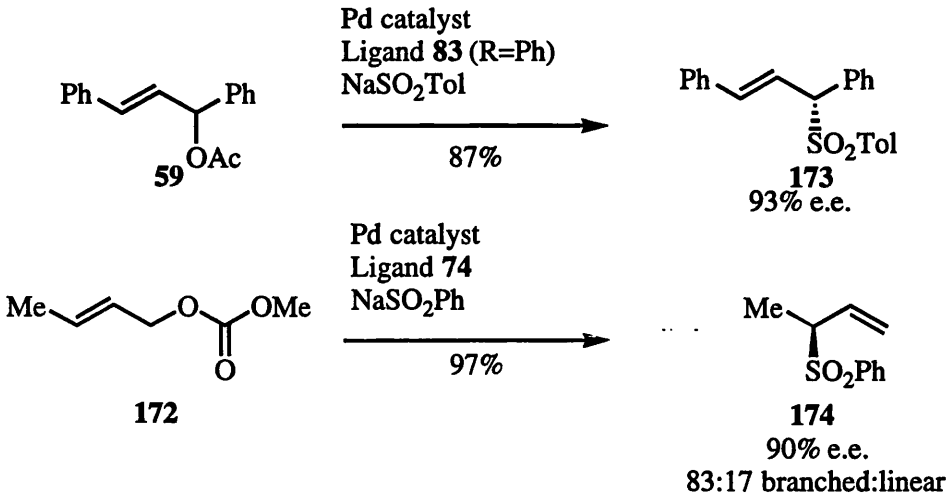
The asymmetric addition of other alcohols is facilitated by the addition of a borane, when epoxide **162** is used as substrate, for instance, the product **170** is formed.[158] The reaction is thought to proceed *via* an intermediate **171**. Trialkylborates have also been used as the source of oxygen nucleophiles. [159]

Scheme 47



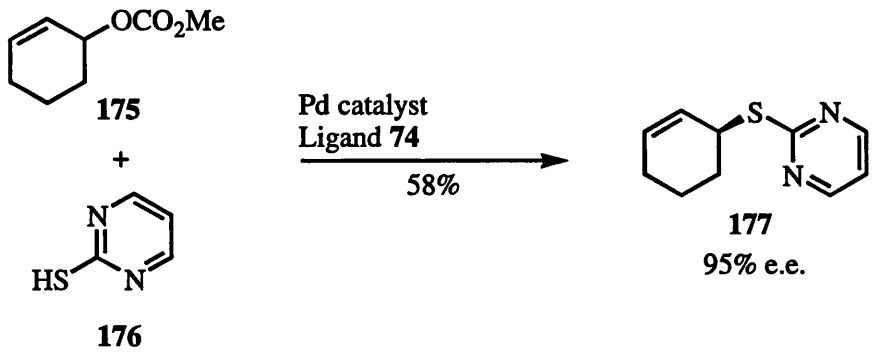
The use of sulfonates as nucleophiles as a method to form enantiomerically enriched allyl sulfones was first reported by Hiroi and Makino in 1986.[160] Acyclic allyl sulfones have been prepared from substrates **59** and **172** under the control of phosphino-oxazoline ligands **83** (R=Ph)[161] or Trost ligand **74**.[162] The reaction has also been applied to cyclic substrates (**Scheme 48**).[163]

Scheme 48



Allylic sulfides can be prepared in a similar fashion, either using silylsulfides (^{t}BuSSiMe$_3$) or free thiols.[164] For example the cyclohexenyl carbonate **175** reacts with thiol **176** to give the allyl pyrimidyl sulfide **177** with excellent enantiomeric excess using the Trost ligand **74** (**Scheme 49**).

Scheme 49



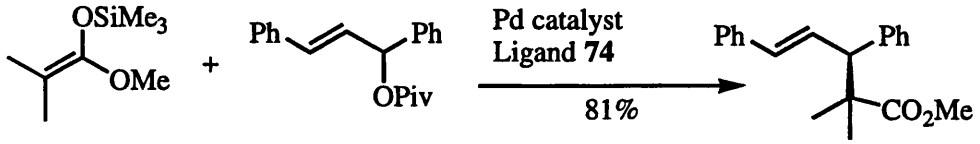
I. Other nucleophiles

In general, stabilised enolates have been used for enantioselective allylic substitution reactions. However the use of ketene silyl acetal **178** has been

reported to react with good enantioselectivity, affording the mono-ester **180** as the product (**Scheme 50**).[165] The anion of nitromethane has also been used successfully as a nucleophile in enantioselective allylic substitution.[166]

Organometallic reagents including Grignard reagents and organozinc compounds have also been used as nucleophiles, although the enantioselectivities reported to date have been unsatisfactory. [167] -[169] It seems that there is plenty of scope for improvement, although nickel complexes have been more widely used than their palladium counterparts, and with reasonable success.[170]-[171]

Scheme 50



178 **179** **180**
90% e.e.

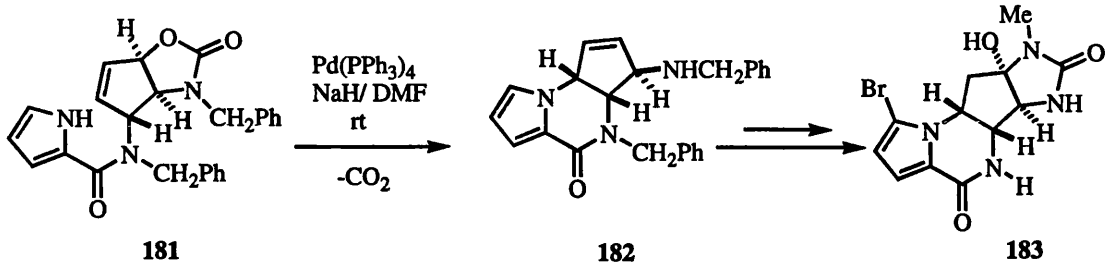
J. Use In Synthesis

Considering the large number of publications involving palladium catalysed allylic substitution reactions, there have been comparatively few examples of its use in synthesis. Most of the efforts have been in the field of cyclisation reactions and the area was reviewed in 1989. [172] These form both C/ C and C/ heteroatom bonds as in the intermolecular variant of the reaction.

For example, in the total synthesis of the antitumor marine sponge alkaloid Agelastatin A, Weinreb[173] utilised palladium promoted cyclisation of amide carbamate **181** to form tricyclic amine **182** as a single stereoisomer. Further elaboration of this compound led to the final product **183** (**Scheme 51**). Although various nitrogen heterocycles including indoles have previously been N-alkylated

with π-allylpalladium complexes, apparently this is the first time a pyrrole has been used in such reactions.

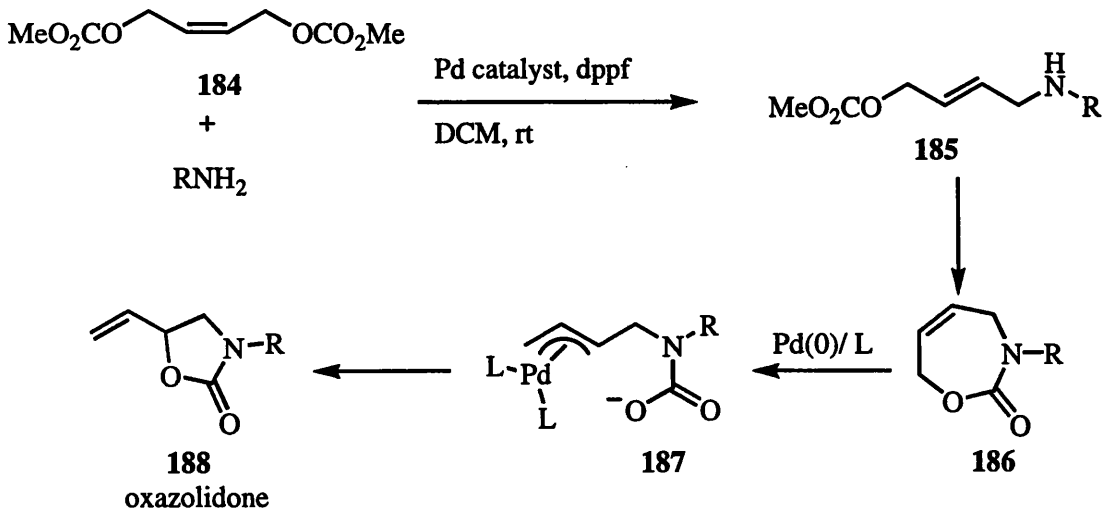
Scheme 51



181 **182** **183**

Synthesis of oxazolidone, using this methodology, has also been reported.[174] This was accomplished using (*Z*)-2-butenylene dicarbonate **184** with primary amines in the presence of Pd catalyst and 1,1-*bis*(diphenylphosphino)ferrocene (dppf). It is believed that the reaction proceeds through the expected substitution product **185** which lactamises to form **186**. Presumably, a second π-allyl formation of the latter gives the observed product **188** (**Scheme 52**).

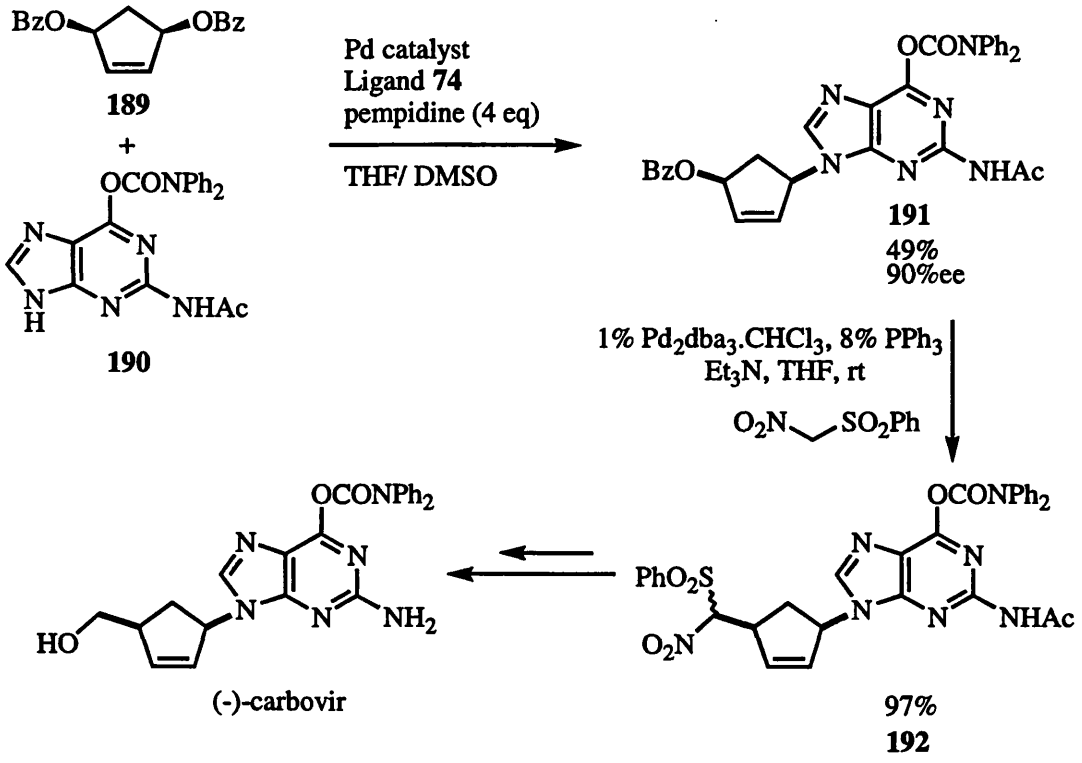
Scheme 52



The shortest synthesis of (-)-carbovir, formed in only six steps, have been achieved by Trost[175] *via* the utilisation of two palladium catalysed allylic

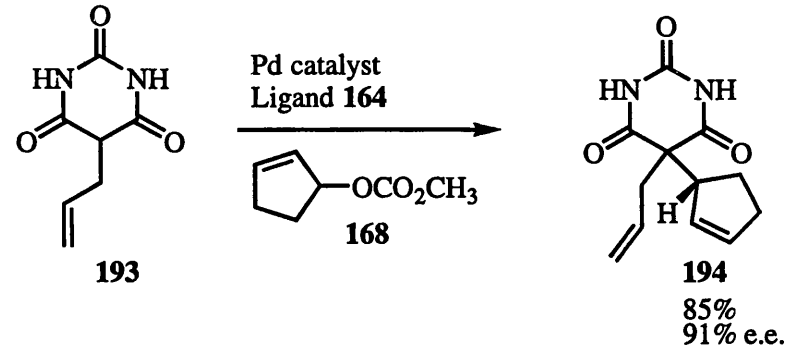
substitutions. This involved Pd-catalysed desymmetrisation reaction of cyclopentadiene **189** with nucleobase **190** and chiral ligand **74** followed by a second palladium catalysed allylic alkylation with phenylsulfonyl(nitro)methane. Carbovir was obtained in two short steps from this compound (**Scheme 53**).

Scheme 53



Palladium catalysed asymmetric allylic alkylation has also been shown to serve as an attractive and economical tool in the synthesis of chiral barbituric acids.[176] High enantio- and regioselectivities have been reported for some reactions. In the synthesis of **194** no di- or tri-alkylation was observed (**Scheme 54**).

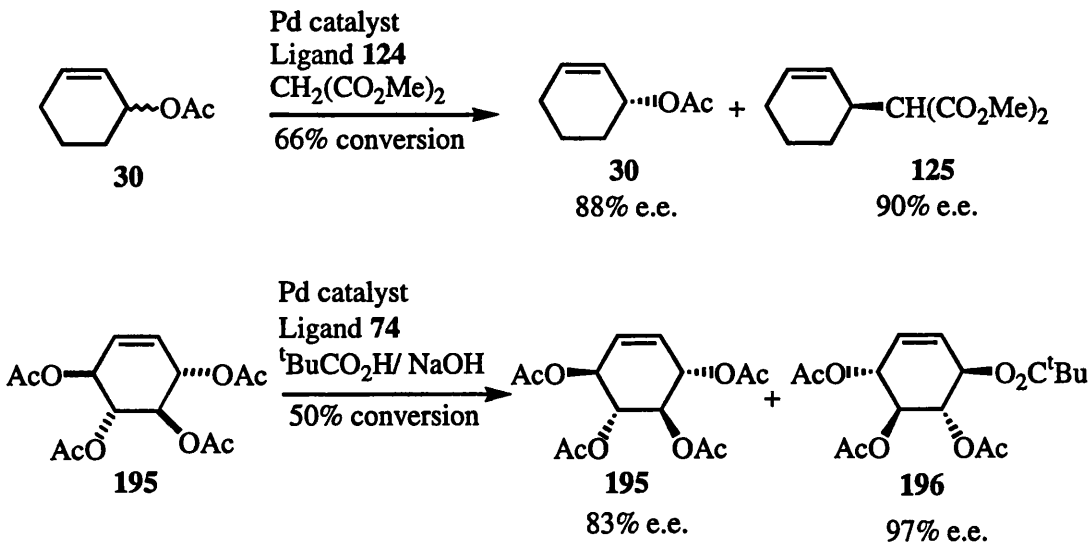
Scheme 54



K. Kinetic Resolution

When a racemic allylic substrate is employed in an enantioselective substitution reaction, one of the two substrate enantiomers may react more quickly than the other. This effect is a kinetic resolution and has been noted reasonably often in enantioselective allylic substitution reactions.[177] Several studies on kinetic resolution have been reported,[178]-[179] and a few highlight reactions are noted in **Scheme 55**. These include recovery of unreacted cyclohexenyl acetate **30**,[180] as well as the tetraacetate **195**.[181]

Scheme 55



L. Other metals

Although the majority of research interest in enantioselective allylic substitution reactions has involved palladium catalysed processes, there have been several successful examples using other metals. These include the use of tungsten,[182]-[183] molybdenum,[184] nickel,[171] iridium,[185] and platinum catalysed reactions.[186]

In summary, palladium catalysed allylation reactions have been achieved with very high enantioselectivities for a wide range of nucleophiles. Many of the best results have been obtained with a handful of 'ideal' substrates. The focus of more recent work has been on synthetically diverse substrates.

Chapter 2

Synthesis of α-Arylpropanoic Acids *via* the Palladium-catalysed Asymmetric Allylic Substitution Reaction

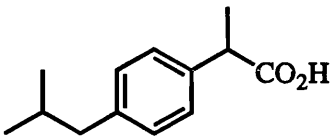
2.1 Background

A vast number of enantiomerically pure 2-arylalkanoic acids, natural as well as synthetic, accomplish useful functions as therapeutic, pest control, and other commercially important agents. The pyrethroid class of pesticides such as fenvalerate, **201**, represent one example of commercial compounds from this family, which are of great importance.[187]

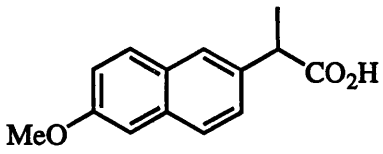
Another example is α-aryl propanoic acids,[188] which have emerged as an important class of non-steroidal anti-inflammatory agents during the past three decades. The important pharmaceutical properties of this class of drugs have been well illustrated by the introduction and extensive use of more than a dozen compounds. Ibuprofen **197**, Naproxen **198**, Ketoprofen **199**, and Flurbiprofen **200** are just a few representative examples (**Scheme 56**).

Intense research into developing synthetic methods for the preparation of these compounds has been carried out by several laboratories, and the increasing number of patents filed by pharmaceutical industries corroborate these efforts.

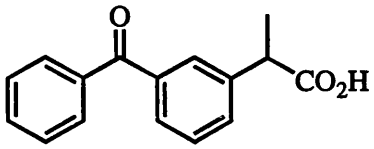
Scheme 56



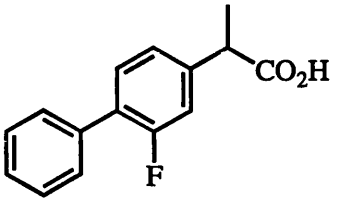
197



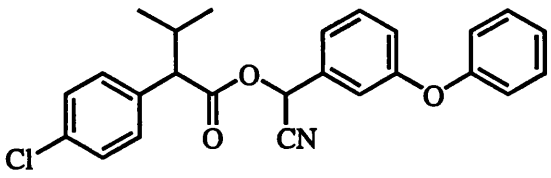
198



199



200



201

However, recently, the use of enantiomerically pure drugs has become increasingly compulsory in an effort to avoid possible toxicity and undesirable strain on the metabolism by the other enantiomer. Hence, pharmaceutical companies are being forced to supply drugs in an enantiomerically pure form.

Coupled with this fact, evidence showing that the pharmacological activity of α-arylpropanoic acids is mainly due to the enantiomer possessing the *(S)*-configuration has considerably raised interest in these compounds.

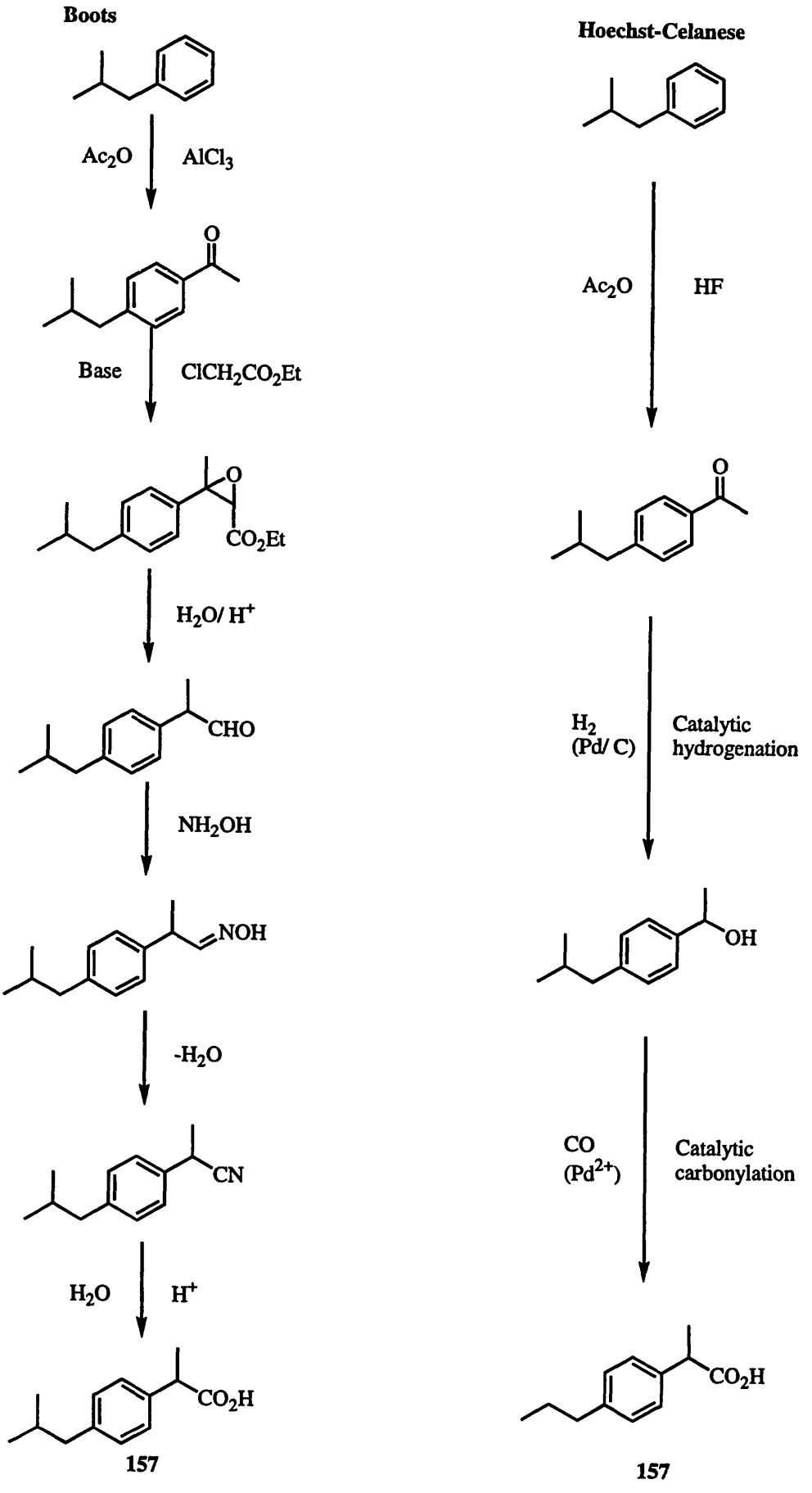
Ibuprofen was introduced into therapy as a non-steroidal anti-inflamatory analgesic for the treatment of rheumatic and allied conditions in the UK in 1969 by the Boots company and in the US by the Upjohn Co. in 1974.[189] It is now being marketed in over 120 countries as the racemic mixture. Two routes for the industrial production of Ibuprofen are illustrated in **Scheme 57**. [190]

It is the *(S)*-enantiomer of Ibuprofen which is the active form and Wechter and Kaiser demonstrated unequivocally that the bioconversion from the *(R)*-(-)-enantiomer to *(S)*-enantiomer takes place in man. [191]

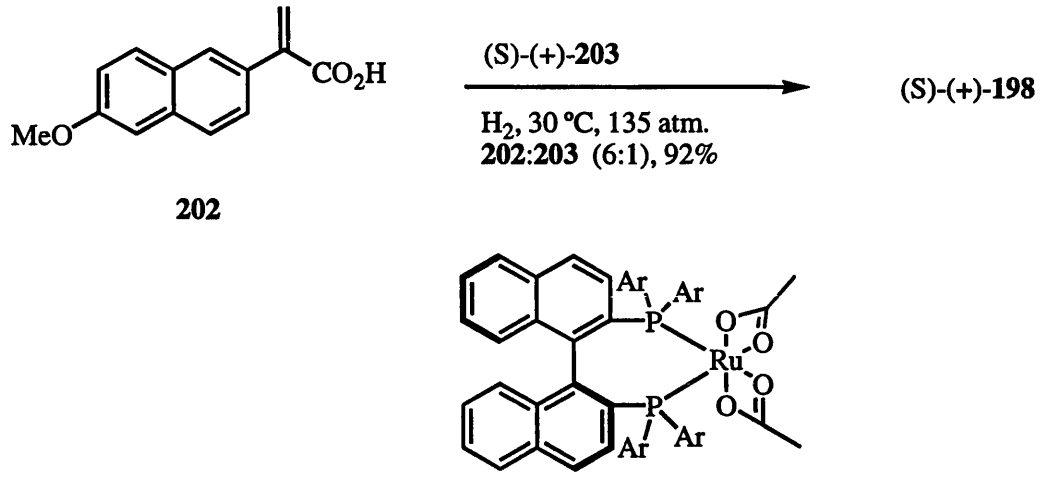
This awareness has encouraged many research groups to devise non-racemic synthesis of Ibuprofen and its analogues. Many methods have been reported including methylation of 2-arylacetic acids, hydrogenation of 2-arylpropenoic acids, metal complex catalysed hydrocarboxylation, hydroformylation of styrenes, hydroxylation of olefins, hydrovinylation, aryl-alkyl coupling reactions, alkylation of aromatics and enantioselective protonations to name just a few. [188]

For example, Noyori et al. [192] have utilised BINAP-ruthenium **203** as the catalyst to obtain (*S*)-(+)-**198** (Naproxen) in 92% yield and 97% ee in the hydrogenation reaction of unsaturated carboxylic acid **202**. Nevertheless, the relatively high pressure (135-150 atm) required for the reaction may present a practical limitation.

Scheme 57


Boots
Ac2O
AlCl3
O
Base
ClCH2CO2Et
O
CO2Et
H2O/ H+
CHO
NH2OH
NOH
-H2O
CN
H2O
H+
CO2H
157
Hoechst-Celanese
Ac2O
HF
O
H2
(Pd/ C)
Catalytic
hydrogenation
OH
CO
(Pd2+)
Catalytic
carbonylation
CO2H
157

Scheme 58

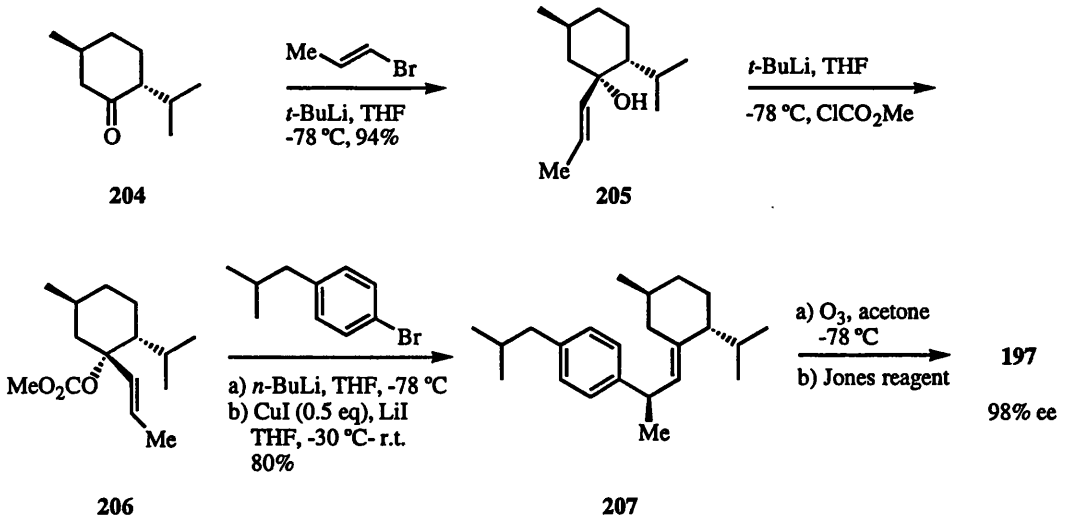


202

(S)-(+)-203

The synthesis of Ibuprofen by Spino et al[193] represents a more recent example. Enantiomerically pure expensive starting material, (+)-menthone (**204**), is used as a chiral auxiliary to assert asymmetry in the final drug molecule *via* relative stereocontrol. Although the starting material can be recycled in 60-70% yield, it would appear relatively uneconomical, although good ee and yield of product are obtained.

Scheme 59



204 **205**

206 **207**

Nevertheless Ibuprofen is still being marketed as the racemic drug as there are no short and efficient methods for the preparation of the single enantiomer.

2.2 Retrosynthesis

In recent years, asymmetric synthetic reactions have received much attention for the creation of new stereogenic centres, especially in the pharmaceutical field. Among the known asymmetric synthetic methods, a catalytic asymmetric reaction with an enantiomerically pure ligand is the most important and challenging method from the point of efficient enantioselectivity.

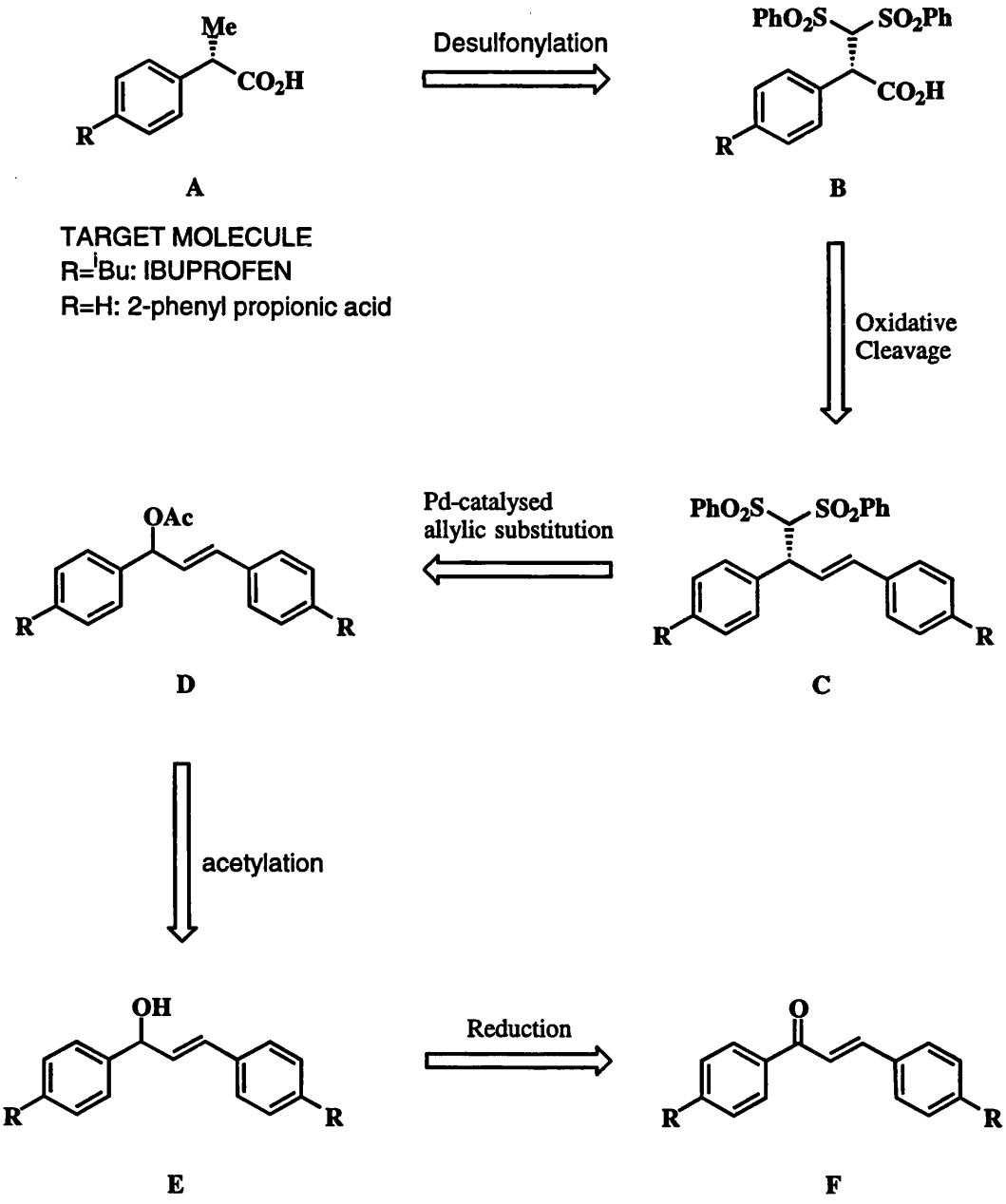
Palladium catalysed allylic reactions using allyl compounds, alkenes and conjugated dienes have been actively investigated as an important synthetic tool for C-C and C-X (X=H, heteroatoms) bond formation and for mechanistic studies. Palladium catalysed asymmetric allylic substitution reactions have been an especially popular topic in the recent years and the flood of publications emanating from various research groups bears testimony to its synthetic uses.

We discussed palladium catalysed allylic substitution reaction in **Chapter 1** in some detail as well as its asymmetric variants, covering the different ligands available to control the selectivity of asymmetric induction.

Our interest lies in utilising 'asymmetric palladium catalysed allylic substitution methodology' towards the synthesis of biologically and therapeutically active compounds. We therefore planned to use this methodology as the key step in the enantioselective synthesis of α-arylpropanoic acids such as *(S)*-**Ibuprofen** and *(S)*-**Naproxen.**

Our retrosynthetic strategy is outlined in **Scheme 60.**

Scheme 60



We envisaged that enantiomerically pure Ibuprofen and its analogues could be synthesised using palladium catalysed allylic substitution as the key step of the synthesis. The target molecule is disconnected to **B** *via* a desulfonylation reaction. This intermediate can be disconnected to compound **C** *via* oxidative cleavage. Compound **C** itself should be available through Pd catalysed allylic substitution and can be disconnected back to allylic acetate **D**. The acetate could in turn be

obtained from the alcohol **E** which should be available from the corresponding ketone.

This retrosynthetic strategy should allow us to synthesise (*S*)-**Ibuprofen** in just five simple steps. As can be seen in the analysis a large number of analogues should also be available *via* the same route, by simply changing the 'R' group in the starting material.

2.3 Model Study-

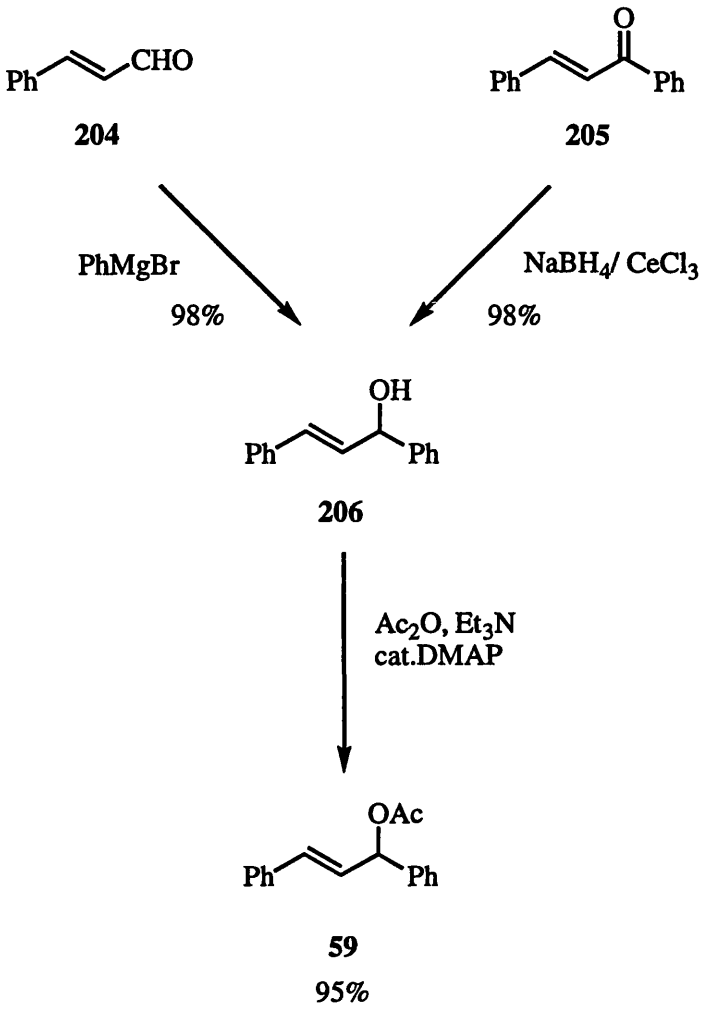
Synthesis of 2-phenylpropanoic acid

Initially a model study was carried out to synthesise 2-phenylpropanoic acid, whereby the 'R' group is a simple hydrogen. The reason behind conducting a model study was to carry out a representative synthesis using cheap and simple starting materials, which would also be simple to analyse. The model study would therefore provide us with the opportunity to develop an efficient synthesis and while doing this to find the optimum conditions for each of the steps. Hence if we obtained a positive outcome from this model study, we would then carry out an enantioselective synthesis of Ibuprofen and its analogues utilising the same methodology.

As discussed in **Chapter 1**, 1,3-diphenylprop-2-enylacetate **59** is the standard substrate for testing different ligand performances in the palladium catalysed allylic substitution reaction.

Racemic 1,3-diphenylprop-2-enylacetate was prepared by two methods. The reaction of phenylmagnesium bromide with cinnamaldehyde formed the alcohol **206**. The same compound can also be formed through the Luche[194] reduction of chalcone **205** with sodium borohydride and cerium trichloride (**Scheme 61**). The reaction can be followed by tlc, which shows the formation of the alcohol spot below the chalcone spot. The reaction is very fast and should be quenched as soon as the starting material spot has disappeared (about 10 min after the addition of $NaBH_4$), as otherwise side products can form, which is evident with the occurrence of extra peaks on ^1H NMR at 5.12 ppm. Product **206** was therefore used in the next step as soon as it was formed.

Scheme 61



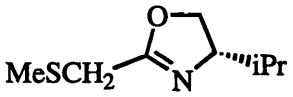
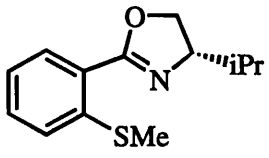
The formation of the alcohol was evident through IR spectroscopy, which showed an OH stretch of 3434 cm^{-1}. Analysis of ^{1}H NMR and ^{13}C NMR spectra also confirmed the structure, by comparison with literature data.

The alcohol **206** was then acetylated using triethylamine and acetic anhydride along with a catalytic amount of DMAP, affording acetate **59**, the substrate for the palladium catalysed allylic substitution reaction. The formation of acetate **59** was confirmed by analysis of the ^{1}H NMR spectra which revealed a three proton singlet at 2.12 ppm assigned to the acetate group and a downfield shift of the sp^3 C-H at 6.44 ppm.

The palladium catalysed asymmetric allylic substitution step is the key step of the synthesis whereby asymmetry is incorporated into the molecule. Genet[195] has demonstrated that sulfone-stabilised carbanions can act as nucleophiles in the palladium catalysed allylic substitution reactions. We decided to use diphenylsulfonyl methane **26** as the soft carbon nucleophile in this part of the synthesis, since once present the sulfone functionality is easily manipulated.[196]

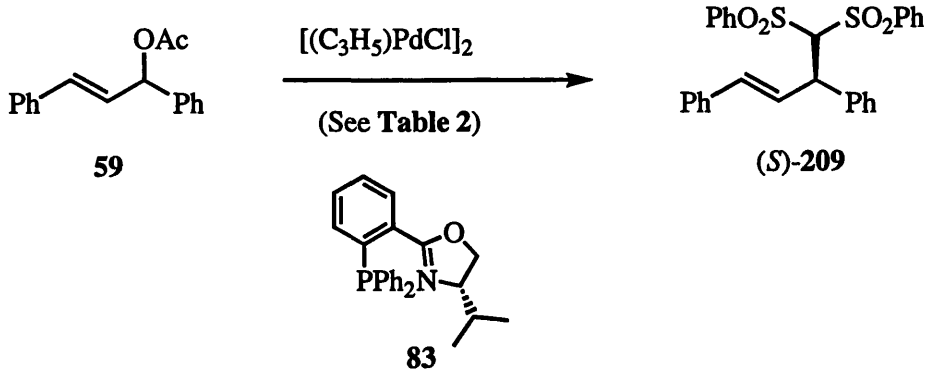
The palladium catalysed allylic substitution reaction was initially attempted using sulfur-based ligands **207** and **208**[197] (**Table 1**). However no product was observed presumably because of the weaker π-acceptor properties of sulfur compared to phosphorus.

Table 1. Enantioselective allylic substitution with *bis*-phenylsulfonylmethane using sulfur based ligands

Ligand	Conditions	Result
 **207**	1. BSA 1.5 eq, KOAc (1 mol%) $(PhSO_2)_2CH_2$ 1.1 eq CH_2Cl_2 40 °C	no reaction
	2. $(PhSO_2)_2CHNa$ 1.1 eq DMF 70 °C	no reaction
 **208**	3. BSA 1.5 eq, KOAc (1 mol%) $(PhSO_2)_2CH_2$ 1.1 eq CH_2Cl_2 40 °C	no reaction
	4. $(PhSO_2)_2CHNa$ 1.1 eq DMF 70 °C	no reaction

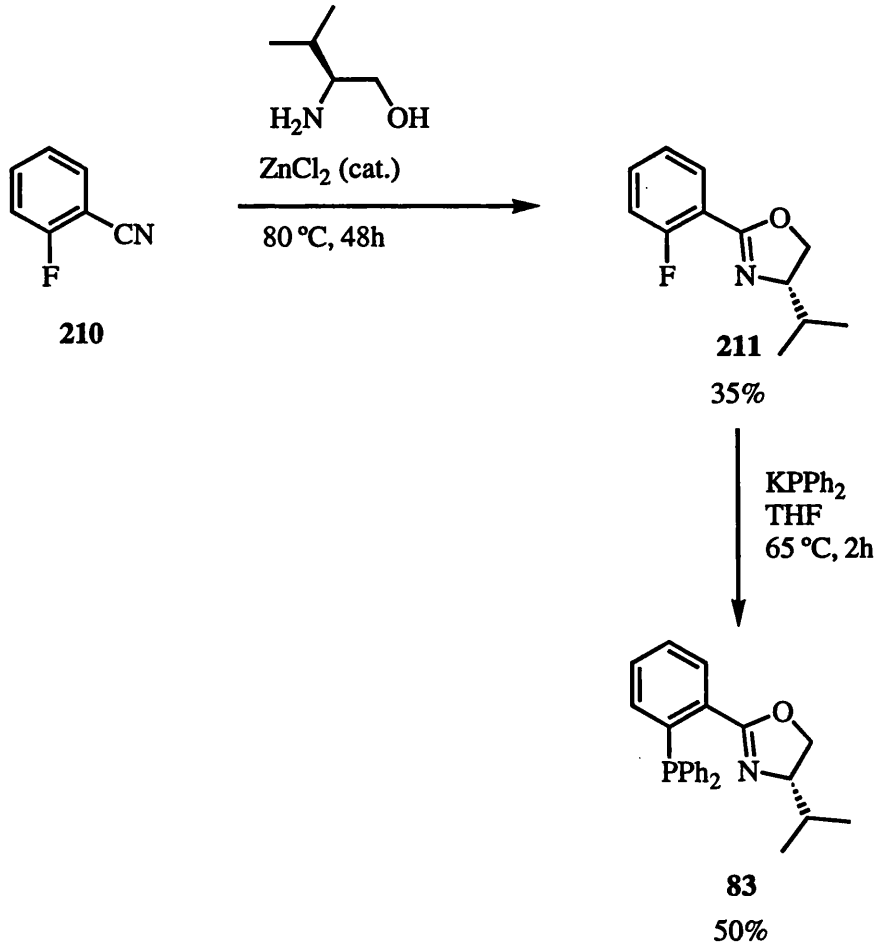
In comparison employing the phospinooxazoline ligand **83,** designed by Williams[85] led to the formation of the substitution product **209 (Scheme 62).**

Scheme 62



The enantiomerically pure phosphinooxazoline ligand **83** was prepared from the fluorooxazoline **211**, following procedures already established within the group. Heating 2-fluoronitrile with (*S*)-valinol in the presence of a catalytic amount of $ZnCl_2$ at 80 °C for 48 hours led to the formation of fluorooxazoline **211**. The reaction of this compound with potassium diphenylphosphide in refluxing THF led to the formation of phosphinooxazoline ligand **83** in 50% yield.

Scheme 63



The results of allylic substitution using this ligand are outlined on **Table 2.**

The reaction of *bis*-phenylsulfonylmethane nucleophile with 1,3-diphenylprop-2-enylacetate is slow, in comparison with the common nucleophile dimethylmalonate, and takes between 24-48 hours to reach completion as well as requiring heat for the reactions to proceed. This observation can be explained, as *bis*-phenylsulfonylmethane is a more sterically encumbered nucleophile. The reaction could be followed by tlc, with the product spot appearing below the starting material. A number of impurities including the disubstitution product were observed on some occasions. Work-up followed by flash column chromatography separated the substitution product from the impurities. In cases where disubstitution was a problem, the crude mixture was columned on alumina, since the separation between product and impurity becomes greater on alumina. The desired product is obtained as colourless needles. Analysis of the ^{1}H NMR spectra showed the disappearance of the acetate peak at 2.12 ppm and a doublet was observed corresponding to $C\underline{H}(SO_2Ph)_2$ at 5.09 ppm which was coupled to the neighbouring allylic proton at 4.71 ppm. Analysis of ^{13}C NMR and accurate mass spectra also confirmed the structure of this compound.

The reaction of acetate **59** with diphenylsulfonyl methane **26** with 5 mol% Pd and 10 mol% oxazoline ligand formed the substitution product in 60% yield and 61% ee (entry 1). In this reaction BSA along with a catalytic amount of CsOAc was used to deprotonate the nucleophile. Altering the ratio of Pd:Ligand from 1:2 to 1:1 seemed to have the effect of lowering the enantioselectivity (entry 2).

We then wanted to test the effect of replacing BSA/ nucleophile with the preformed sodiodiphenylsulfonyl methane on the outcome of the reaction.

However since the sodiodiphenylsulfonyl methane salt is not very soluble in THF, we were forced to add more solvent into the reaction, thereby diluting it (entry 3). Nevertheless this reaction also gave lower ee in comparison with the conditions in entry 1. However the sodium salt of the nucleophile was more soluble in DMF, therefore DMF was also tested as a solvent. This reaction gave a much higher ee of 78%. However the yield of the reaction was lower (entry 4).

On the other hand, the reaction of sodiodiphenylsulfonyl methane nucleophile in THF at the higher temperature of 85 °C had the effect of improving the yield to 75% while ee remained at 61% (entry 5).

The reaction was also carried out in 1,4-dioxane using 1:1 Pd to Ligand. We found that the sodium salt of the nucleophile **26** was not very soluble in this solvent although it eventually dissolves when heated at 70 °C. After 24 h. this reaction formed the desired product in 70% yield and 65% ee (entry 6).

However best enantioselectivities were obtained when 2.5 mol% Pd and 5 mol% ligand were used. Increasing the concentration of the reaction increased the yield and ee (compare entries 7 and 8). A yield of 50% and a very good ee of 87% were obtained under the reaction conditions outlined in entry 8.

Table 2. Enantioselective allylic substitution with *bis*-phenylsulfonylmethane using oxazoline ligand **83**.

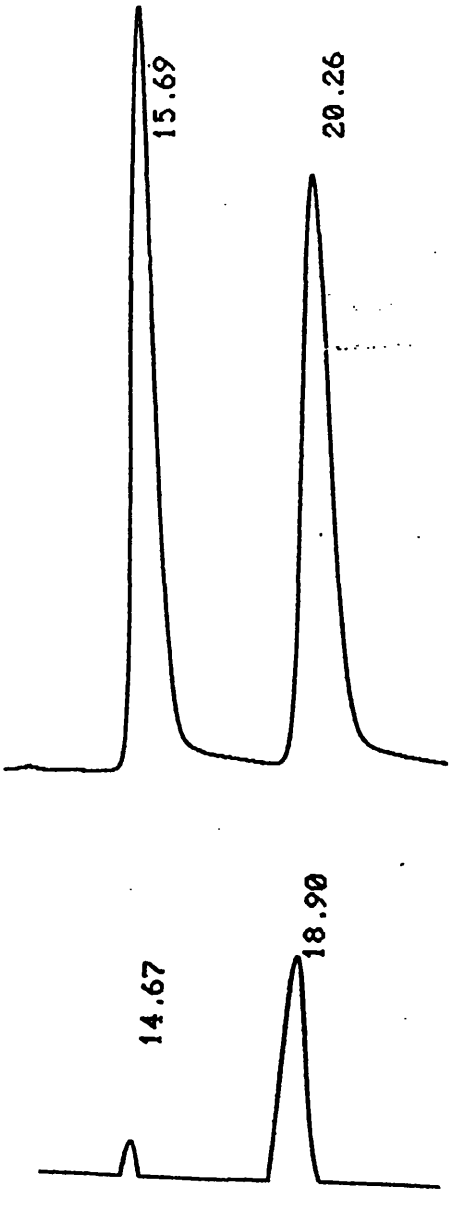
Entry	Catalyst	Solvent	Temp. (°C)	Nucleophile/ Base	Yield %	ee %
entry 1	5 mol% Pd 10 mol% **83**	THF[a]	73	BSA/ **26** CsOAc	60	61
entry 2	5 mol% Pd 5 mol% **83**	THF[a]	73	BSA/ **26** CsOAc	60	31
entry 3	5 mol% Pd 10 mol% **83**	THF[b]	73	$NaCH(SO_2Ph)_2$	65	34
entry 4	5 mol% Pd 10 mol% **83**	DMF[a]	73	$NaCH(SO_2Ph)_2$	40	78
entry 5	5 mol% Pd 10 mol% **83**	THF[a]	85	$NaCH(SO_2Ph)_2$	75	61
entry 6	6 mol% Pd 6 mol% **83**	1,4-dioxane[b]	70	$NaCH(SO_2Ph)_2$	70	65
entry 7	2.5 mol% Pd 5 mol% **83**	THF[c]	73	BSA/ **26** CsOAc	33	80
entry 8	2.5 mol% Pd 5 mol% **83**	THF[d]	73	BSA/ **26** CsOAc	50	87
entry 9	2.5 mol% Pd 5 mol% dppe	THF[d]	73	BSA/ **26** CsOAc	84	-

[a] Carried out at a substrate concentration of 0.16 mmol/ mL.
[b] Carried out at a substrate concentration of $6x10^{-2}$ mmol/ mL.
[c] Carried out at a substrate concentration of 0.13 mmol/ mL.
[d] Carried out at a substrate concentration of 0.26 mmol/ mL.

The e.e. was determined by HPLC using a chiral AD column. The racemic product was also synthesised using dppe as the ligand, *via* the same procedure, in order to identify both of the enantiomers on HPLC.

HPLC analysis of compound (±)-**209** and (*S*)-**209**

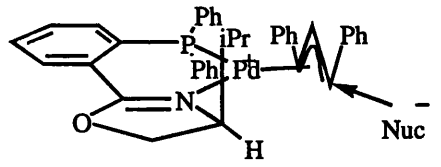
Chiral AD column, 70:30 Hexane:IPA, 1mL/ min.

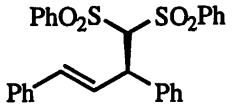


As explained in **Chapter 1**, the ability of ligand **83** to promote nucleophilic attack to one terminus is a consequence of the difference arising from the electronic properties of the donor atoms. There are four possible diastereomeric complexes, **212** to **215**, which could give rise to the expected product. Two of these predict the correct enantiomer of product (**Scheme 64**).

The nucleophile is expected to approach the allyl complex *trans* to the phosphorus, which is the better π-acceptor, resulting in complex **212** or **214** (Akermark).[198] In addition, the π-allyl complex can adopt an 'M' orientation or a 'W' orientation. This implies that the stereochemistry of the product could be controlled if the allyl group could be fixed in either the 'M' or the 'W' orientation. In a number of X-ray crystallographic and NMR studies, research published by Helmchen[199] has demonstrated that complex **212** ('W' orientation) was the major diastereomer in equilibrium. This is in agreement with the product we observe and serves to explain the origin of enantioselectivity.

Scheme 64



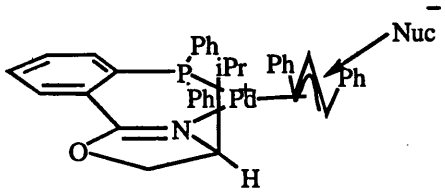


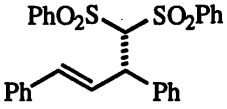
observed enantiomer

212

W-orientation

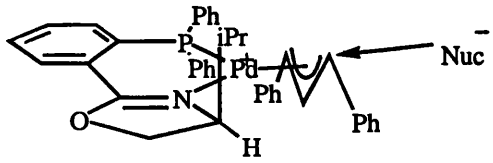
Nucleophilic addition to this complex leads to the observed enantiomer of product.

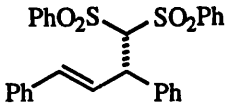




213

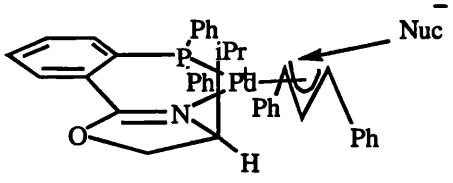
W-orientation

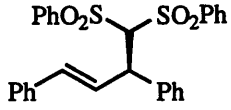




214

M-orientation





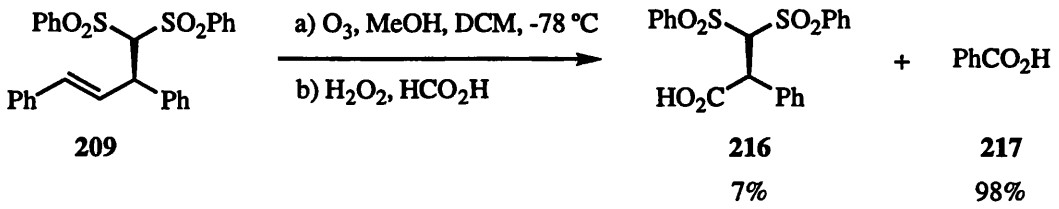
215

M-orientation

The next step of the synthetic plan was to cleave the C=C bond oxidatively in compound **209**, in order to obtain the corresponding carboxylic acid **216**. The desulfonation of this compound would then afford the target molecule.

The ozonolysis reaction of compound **209** was carried out in a mixture of MeOH and DCM, followed by oxidative work up. The reaction was repeated several times varying the proportions of MeOH and DCM as well as the amount of O_3 bubbled through. However the desired product was isolated in just 7% yield as a colourless solid (**Scheme 65**).

Scheme 65



209 **216** **217**

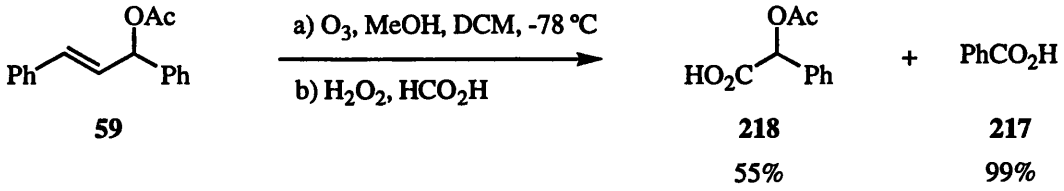
7% 98%

Once the reaction was complete the carboxylic acid portion of the product mixture was extracted using 1M NaOH and acidifying the aqueous layer, followed by back extraction into the organic layer using DCM. The disappearance of the allylic protons at 6.25 ppm and 6.85 ppm and the appearance of a doublet at 4.59 ppm corresponding to $C\underline{H}CO_2H$ and at 5.71 ppm ($C\underline{H}(SO_2Ph)_2$), the two protons being coupled to each other, identified the compound to be carboxylic acid **216**. In addition, the product was observed on the baseline of the tlc plate using DCM, whereas it revealed an R_f of 0.63 when 5% acetic acid/ DCM was used, appearing below the benzoic acid spot (R_f 0.81). The desired product was separated from the by-product of the reaction, benzoic acid, by flash column chromatography.

One of the problems with this reaction was that the starting material, **209**, being a very polar compound as well as incorporating four phenyl groups, was insoluble in MeOH as well as a large range of other solvents. Therefore DCM was added into the reaction in an attempt to solublise the starting material. Nevertheless solubility was a problem under the reaction conditions at -78 °C. Another problem might have been the steric hindrance of the bulky sulfone groups on the molecule. The reason for this argument is that starting material was visible by tlc even after the reaction solution had turned blue revealing that the solution was saturated with ozone. On the other hand the formation of benzoic acid in 98% yield shows that 98% of the substrate was cleaved.

We were curious to find out whether the problem could be stemming from the presence of sulfonyl groups. We therefore carried out the ozonolysis reaction on 1,3-diphenylprop-2-enylacetate **59**. The carboxylic acid portion of the crude product was isolated by extracting with 1M NaOH, followed by acidification and back-extraction into DCM. Analysis of this carboxylic acid portion of the crude mixture showed the presence of compound **218** which was isolated in 55% yield as a yellow oil, although this is not optimised and therefore the actual yield could be higher (**Scheme 66**). The structure of the product was elucidated by ^{1}H NMR analysis, which showed no trace of the allylic protons at 6.30 ppm and 6.63 ppm. The proton C<u>H</u>OAc was observed to shift from 6.44 ppm to 5.93 ppm. Interpretation of the ^{13}C NMR spectra showed the carboxylic acid carbon to be at 177.8 ppm. Therefore, it was shown that carboxylic acid, **218** could be obtained by the ozonolysis reaction of **59** followed by oxidative work-up.

Scheme 66

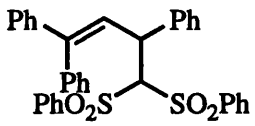


59 **218** **217**

55% 99%

We envisaged that by slightly altering the structure of substrate allylsulfone **209**, we could get around the problem of solubility. Therefore, adding an extra phenyl group to the allylic carbon of compound **209** could make this compound more soluble in aprotic or non-polar solvents therefore allowing the ozonolysis reaction to take place in a larger range of solvents.

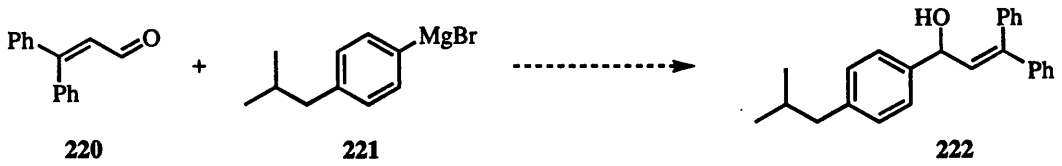
Scheme 67



219

One of the other advantages of using this compound, **219**, rather than **209**, would be in its ease of accessibility, thereby making it easier to introduce the different 'R' groups in the arylpropanoic acids (e.g. isobutyl group in the case of Ibuprofen). This would therefore allow the preparation of a large range of analogous allylic alcohols by simple reaction with Grignard reagents, for instance by the reaction of isobutylphenyl magnesiumbromide **221** with β-phenylcinnamaldehyde **220** (**Scheme 68**).

Scheme 68

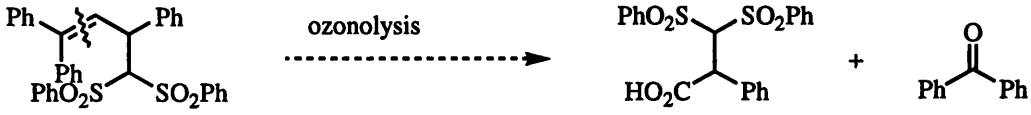


220 **221** **222**

The resulting alcohol would then be acetylated to undergo the palladium catalysed nucleophilic substitution reaction to give the corresponding allyl sulfone.

Another advantage of using disubstituted alkene **219**, would be that its ozonolysis would be expected to produce benzophenone **224** (rather than benzoic acid), as well as the desired product **223**. This would remove the problem of separating two carboxylic acids.

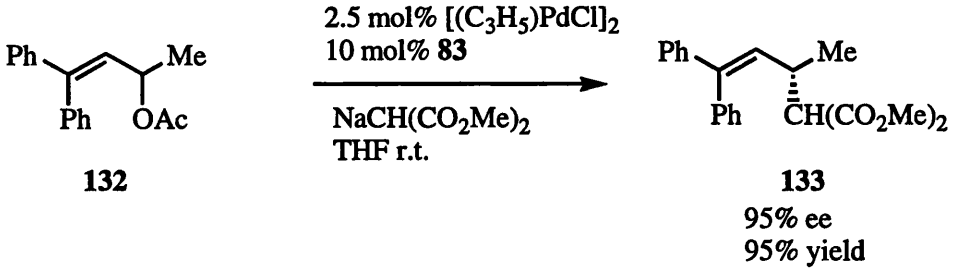
Scheme 69



219 **223** **224**

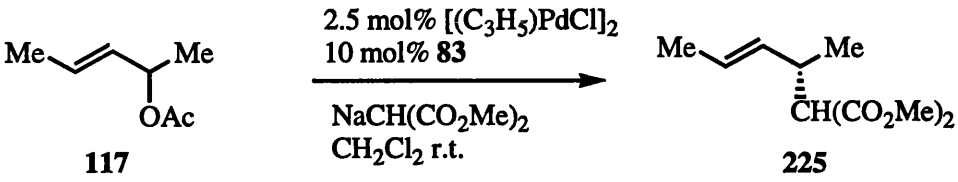
In addition, unsymmetrical allyl systems have been reported to give enhanced enantioselectivity in palladium catalysed allylic substitution reactions, compared with their counterparts containing identical termini. This is particularly striking in the comparison of the enantioselective palladium catalysed allylic substitution reaction of substrates **132** and **117**.[132] It has been suggested by Williams that the reason for this increase in enantioselectivity could be a result of the bulky diphenyl terminus of the allyl systems interacting more with the ligand and helping to position the allyl intermediate into one conformation (**Scheme 70**).

Scheme 70



132 **133**

95% ee
95% yield

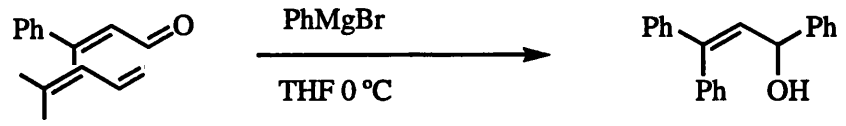


117 **225**

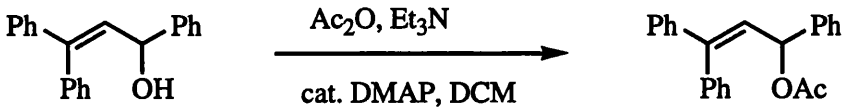
62% ee
52% yield

An attempt was therefore made to synthesise compound **219**. Its precursor was prepared by the reaction of phenyl magnesium bromide with β-phenylcinnamaldehyde. This led to the formation of alcohol **221** in quantitative yield, which was then acetylated with acetic anhydride, a catalytic amount of DMAP and Et_3N. Acetate **132** was obtained as a white solid in 88% yield (**Scheme 70**). Analysis of the ^1H NMR spectrum revealed the acetate singlet to appear at 2.04 ppm. In addition, ^{13}C spectrum displayed a signal at 169.6 ppm suggesting the presence of C=O, which was in agreement with the literature values.[132]

Scheme 71



220 **221**
quantitative



221 **132**
88%

Unfortunately the palladium catalysed allylic substitution on substrate **219** failed, using diphenylsulfonyl methane as the nucleophile, and starting material was recovered from the reaction. This might have been because of the extra phenyl group, which would allow more of the allylic electrons to be delocalised hence making the molecule less attractive for nucleophilic attack. Another suggestion might be the conformational instability of the molecule because of the steric interactions of the two hydrogens on the two phenyl groups. This was not altogether surprising since 1,1-diphenylallyl acetates have also been reported to be less reactive than their symmetrically substituted counterparts, in other literature examples.[132]

This result urged us to look at other methods of oxidatively cleaving the C=C bond in compound **209.**

Although aldehydes are obtained from the cleavage of double bonds by ruthenium tetroxide under neutral conditions, carboxylic acids are produced under alkaline or acidic conditions.[200] For example, the oxidation of cyclohexene by

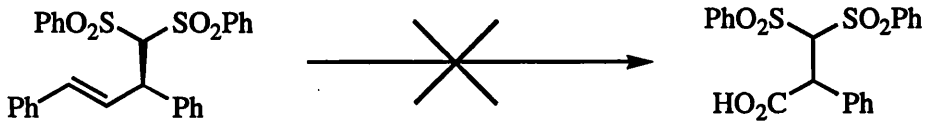
RuO_4 under alkaline conditions has been reported to give adipic acid in yields of 86-95%.[201]

When RuO_2 or $RuCl_3$ is used to catalyse periodate cleavages, it is likely that RuO_4 is first formed which then reacts with the double bond.

Sharpless[202] has demonstrated that the best solvent system for this reaction is a mixture of carbon tetrachloride, acetonitrile and water, in a volume ratio of 2:2:3.

Since ozonolysis with oxidative work up did not give the desired result, an attempt was made to cleave the C=C bond in **209** oxidatively using RuO_4 (**Scheme 72**) using a modified version of the Sharpless procedure to adapt it to our substrate, replacing CCl_4 with DCM or ethyl acetate. In both cases the reaction proceeded, however almost none of the desired product was obtained, as observed by tlc and ^1H NMR analysis. The latter one showed singlets around the aldehyde region (9-11 ppm) as well as many signals around 7-8 ppm where aromatic protons would be observed. Hence it would be reasonable to suggest that this method resulted in the cleavage of the phenyl rings and in the formation benzaldehyde.

Scheme 72



209 **216**

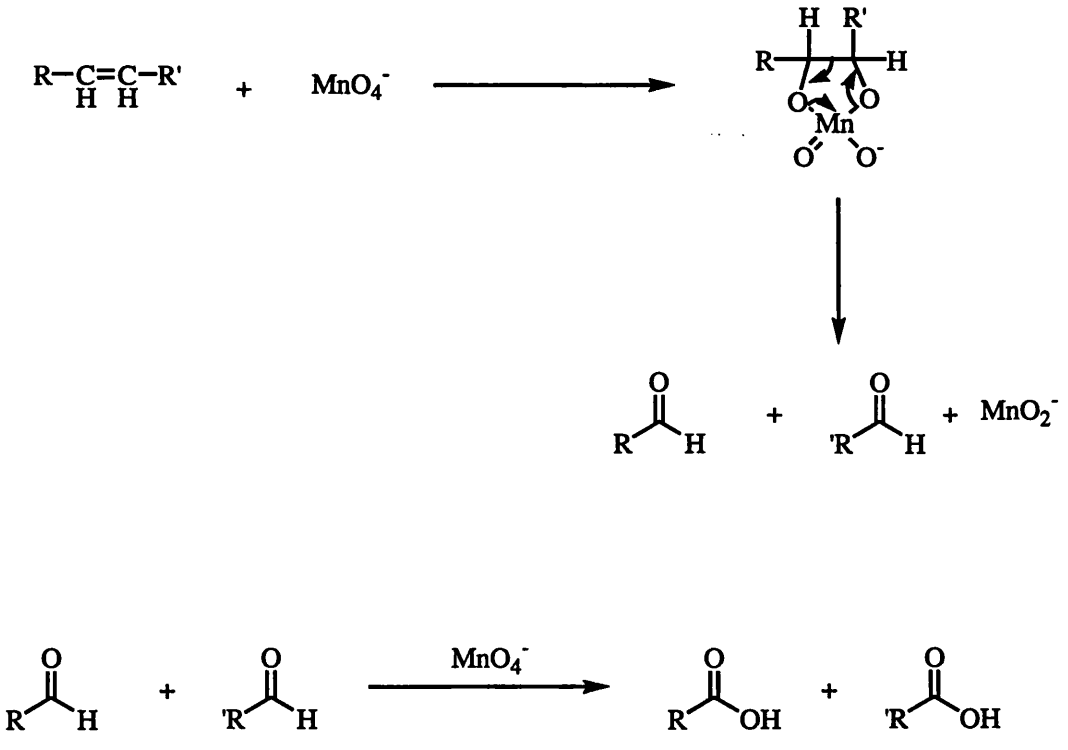
Conditions: $RuCl_3$, $NaIO_4$, EtOAc/ MeCN/ H_2O
and $RuCl_3$, $NaIO_4$, DCM/MeCN/H_2O

An alternative method was to use potassium permanganate. In aqueous solutions permanganate readily oxidises water-soluble alkenes.[203] However the nature of the products depend on the reaction conditions. In acidic solutions cleavage

reactions predominate;[204] under basic conditions, dihydroxylation is the main reaction;[205] and in a neutral media ketols are formed as the major product.[206] Unfortunately the conditions under which these reactions take place, are not sharply defined and mixtures of products are often obtained. However, it is generally possible to predict what will be the major product of a reaction under a particular set of conditions. It is known that the initial reaction between alkene and permanganate results in the formation of a cyclic manganate (V) diester **(Scheme 73)**.

Under acidic conditions, manganate (V) diester apparently undergoes an oxidative decomposition that results in cleavage products plus manganate.

Scheme 73



However, since many alkenes lack sufficient solubility in water and since potassium permanganate is not soluble in organic solvents, co-solvents such as

pyridine, acetone or acetic acid have often been used to bring the oxidant and reductant into contact.

We carried out the Lemieux-Von Ruoloff reaction,[207] whereby $KMnO_4$ was used along with sodium periodate, in an endeavour to form compound **216** (**Scheme 74**). This technique involves the use of a catalytic amount of $KMnO_4$ in a buffered solution of sodium metaperiodate. The double bond is attacked by the permanganate, which is continually being regenerated from its reduced state by the periodate.

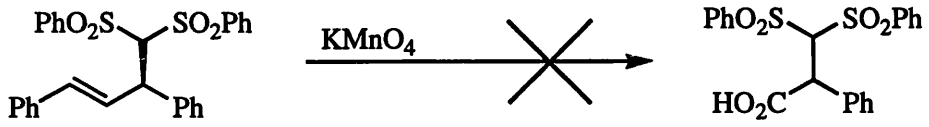
0.2 eq. of $KMnO_4$ was used along with $NaIO_4$ and potassium carbonate in a 7:3 mixture of *tert*-butyl alcohol and water. This was added to a solution of the substrate in DCM and *tert*- butyl alcohol. Since the substrate was not soluble in *tert*-butyl alcohol, DCM was added to increase solubility. As the reaction proceeded the dark purple colour of the permanganate was discharged. However, after stirring the reaction overnight, ^1H NMR analysis revealed that starting material had not reacted. Hence no reaction was observed and starting material was recovered from this reaction.

An alternative method of solublising permanganate in organic solvents is the use of phase transfer agents. Karaman[208] has observed that both quaternary ammonium and phosphonium salts as well as polyethers could be used for this purpose.

Hence two reactions were carried out with the phase transfer catalysts dibenzo-18-crown-6, and Adogen 646 (**Scheme 74**). In both cases according to ^1H NMR the amount of starting material and the amount of the desired product were negligible as judged by the integrations. However, there were many aromatic protons present

between 7-8 ppm. In addition there were several spots observable upon the tlc plate.

Scheme 74



209 **216**

Conditions: - $NaIO_4$, DCM, *t*BuOH/ H_2O

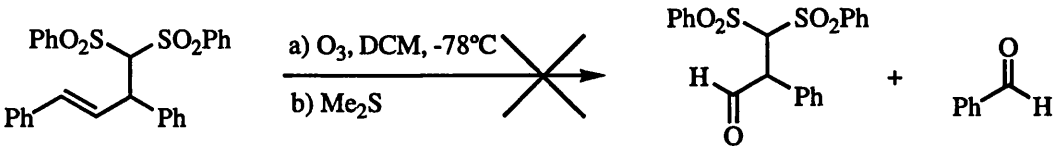
AcOH, dibenzo-18-crown-6

Adogen 646, AcOH, DCM

Since the attempted oxidative cleavage reactions did not give the desired product, an attempt was then made to produce the sulfonated aldehyde **226** (**Scheme 75**), which could then be oxidised to the desired carboxylic acid.

The ozonolysis reaction was therefore quenched with dimethylsulfide. The reaction formed a number of products. Benzaldehyde was formed in high yield. The desired product **226** was not formed as judged by ^{1}H and ^{13}C NMR analysis.

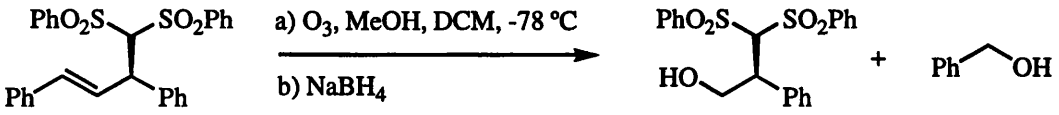
Scheme 75



209 **226** **227**

We decided to turn our attention to ozonolysis with a reductive work up, which was carried out in order to obtain the sulfonated alcohol **228**. If this reaction gave a high yield of the alcohol, it could then be oxidised to the corresponding carboxylic acid target molecule.

Scheme 76



209
80% ee

228
89%
80% ee

229
90%

A batch of allylic sulfone (*S*)-**209** of 80% ee obtained from the palladium catalysed asymmetric allylic substitution step was carried forward onto the next step of the synthesis. A batch of racemic substitution product **209** was also taken forward onto the next step. Racemic synthesis and enantiopure synthesis were therefore carried out side by side in order to synthesise both racemic and enantiomerically enriched products in all of the steps of the synthesis of 2-phenylpropanoic acid.

The ozonolysis reaction took place at –78 °C and $NaBH_4$ was used to quench the reaction in order to obtain the sulfonated alcohol. The desired product was isolated in 89% yield as a colourless solid and the by-product, benzyl alcohol, in 90% yield. The structure of alcohol **228** was identified by analysis of ^1H NMR spectrum, judged by the formation of a singlet at 2.28 ppm corresponding to the OH proton and the presence of two protons at 4.32 ppm ($C\underline{H}_2OH$) as a multiplet. ^{13}C NMR also showed the presence of CH_2OH at 62.08 ppm and the presence of two carbons attached to a proton at 47.45 ppm and 88.89 ppm. Hence the alcohol was synthesised in good yield and was ready for desulfonylation and oxidation to form the carboxylic acid target molecule.

At this stage of our synthesis of 2-phenyl propanoic acid **231**, the sulfone group in alcohol **228** had to be removed and the alcohol functionality would then be oxidised.

Organic sulfur chemistry is a powerful tool in organic synthesis because of the unique properties of sulfur, derivatives of which are reactive, and versatile synthons. Since it is easy to remove the sulfur at the end of the synthesis *via* reductive cleavage of a C-S bond, it is used widely in organic synthesis.

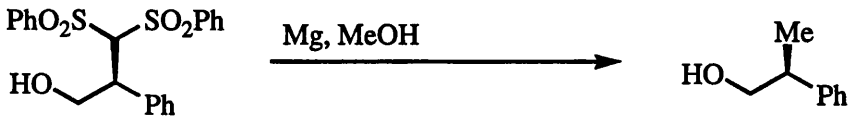
Among the reagents used to remove sulfone groups are Raney Ni,[209] hydrides or organometallics combined with transition metal salts or their complexes such as $[(Cp_2NiAlH_2)–Li^+]_2$.[210] Electropositive metals have also been used to cleave C–S bonds. Alkali metals[211] are the most commonly used, but Mg, Ca, and Zn are also utilised for this purpose. Single electron transfer takes place during these desulfurisations. Also amalgams such as [Na(Hg)][212] used in excess in alcoholic solvents are known to desulfurise sulfones. Tin hydrides are also among the reagents used.

Our choice for the desulfonylation of compound **228** was to use Mg in MeOH. This would be free from the problems associated with the toxicity of Sn and Hg and the drawbacks of Raney Ni such as expensiveness and short 'shelf-life'.

Modification of a procedure by Carpino[213] was applied to desulfonylate alcohol **228** (**Scheme 77**). Activated Mg turnings heated at 50 °C in MeOH led to the generation of hydrogen gas and ultimately to the reduction of the sulfonyl functionalities. Product **230** was obtained in 65% yield as a yellow oil. The structure was proven using ^1H NMR analysis, which showed the presence of methyl peak at 1.25 ppm. A comparison with the literature values also showed that we had made the expected compound.[214] ^{13}C NMR analysis also showed the

presence of methyl carbon at 17.54 ppm. Information obtained from IR spectroscopy supported the proposed structure. HPLC analysis using chiral OB column showed the enantiomeric excess to be 80%.

Scheme 77



228
80% ee

230
65%
80% ee

The final step was to oxidise 2-phenylpropan-1-ol **230** to obtain the corresponding carboxylic acid.

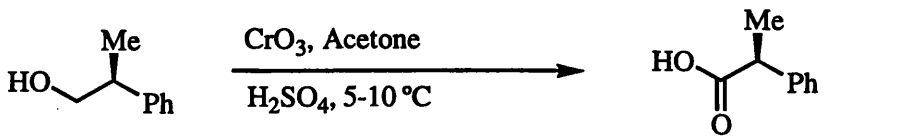
Chromium reagents are the most widely used for the oxidation of primary alcohols into carboxylic acids. However, there are a number of problems associated with the use of chromium such as its toxicity and the problem of its removal from the product. Therefore there has been an interest in the development of methods for the use of catalytic and supported reagents.

One of the best-known and most widely used methods of oxidation using chromium(VI) is the Jones oxidation[215] which utilises an aqueous sulfuric acid and acetone solvent system. Acetone is said to perform a dual role in that it is an excellent solvent for a wide range of organic molecules and it protects the substrate from over oxidation or undesired side reactions by reacting with the excess oxidant itself. Hence it is uncommon to observe substantial epimerisation of α-chiral centres.[216] Secondary alcohols are converted into ketones in good

yields,[217] whereas primary alcohols are usually converted into the corresponding acids.[218]

The oxidation reaction was carried out by Jones oxidation. The desired product **231** was formed in 77% yield and HPLC analysis was determined the enantiomeric excess to be 80% e.e. (**Scheme 78**). The structure was elucidated using ^{1}H NMR, ^{13}C NMR and IR spectroscopy and a comparison with literature values indicated the structure to be correct.[219] ^{1}H NMR analysis showed the presence of the methyl group at 1.48 ppm coupled to a neighbouring CH proton. The carboxylic carbon was observed at 180.69 ppm in ^{13}C NMR. IR spectroscopy also showed the presence of the OH band at 3030 cm^{-1} and C=O stretch at 1705 cm^{-1}.

Scheme 78



230
80% ee

231
2-phenyl propanoicacid
77%
80% ee

We carried out both the racemic and asymmetric synthesis of 2-phenylpropanoic acid side by side, using the same retrosynthetic route.

In conclusion, we proved with this model study that 2-phenylpropanoic acid could be synthesised in high yield and good enantiomeric excess, using the asymmetric palladium catalysed allylic substitution as the key step. We were pleased to find that the final product was synthesised without loss of enantiomeric purity, i.e. no epimerisation was observed.

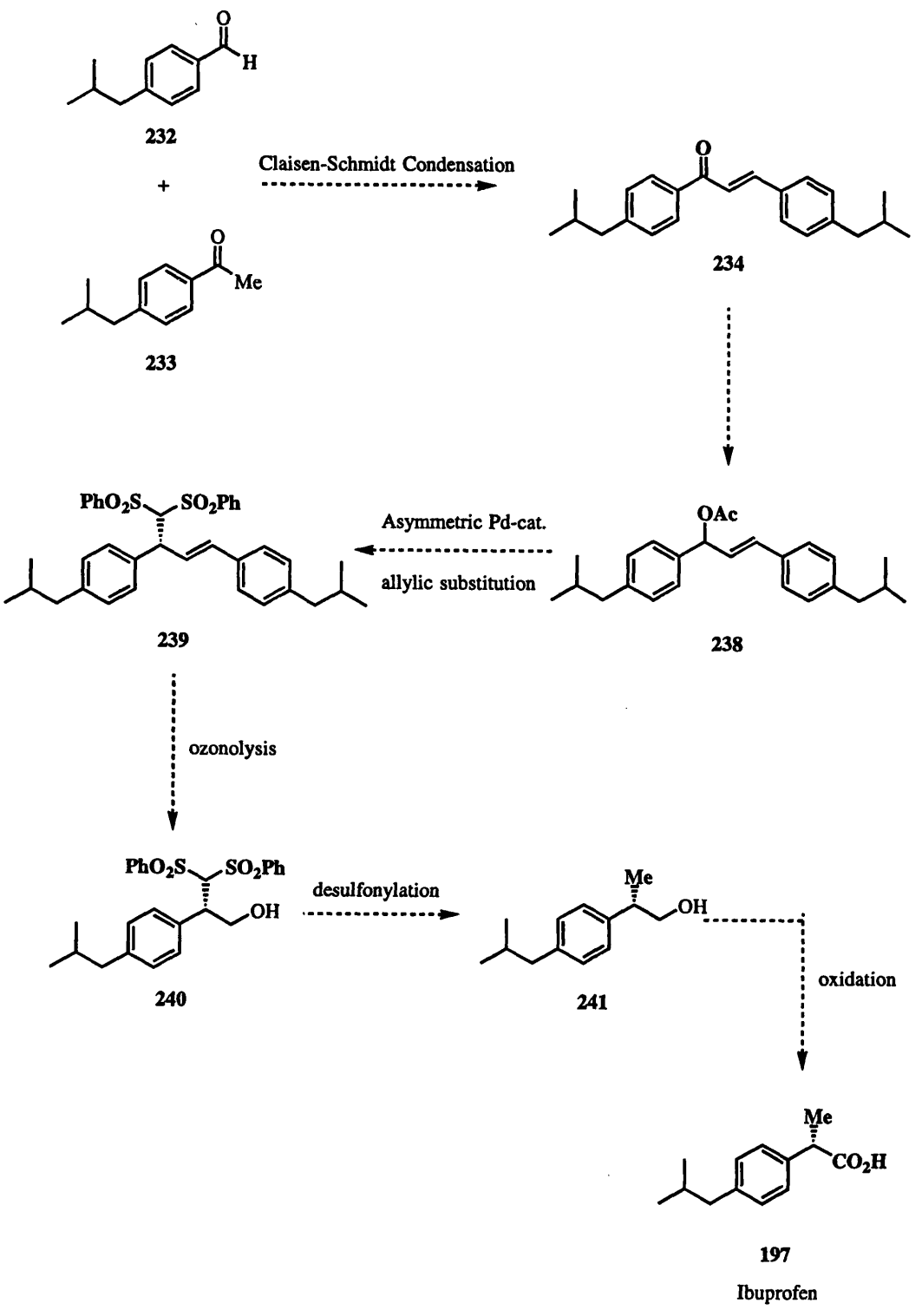
Although the proposed route of cleaving the C=C bond in compound **209** to obtain the sulfonated carboxylic acid **216** did not work, despite several attempts using a wide range of reagents; this problem was partially resolved by cleaving the double bond *via* ozonolysis followed by a reductive work up. Hence the alcohol **228** was obtained rather than the carboxylic acid. Therefore an additional step was added to the synthesis by having to oxidise the alcohol to the carboxylic acid. The synthesis of enantiomerically enriched Ibuprofen should be straightforward *via* the same route.

2.4 Asymmetric Synthesis of Ibuprofen

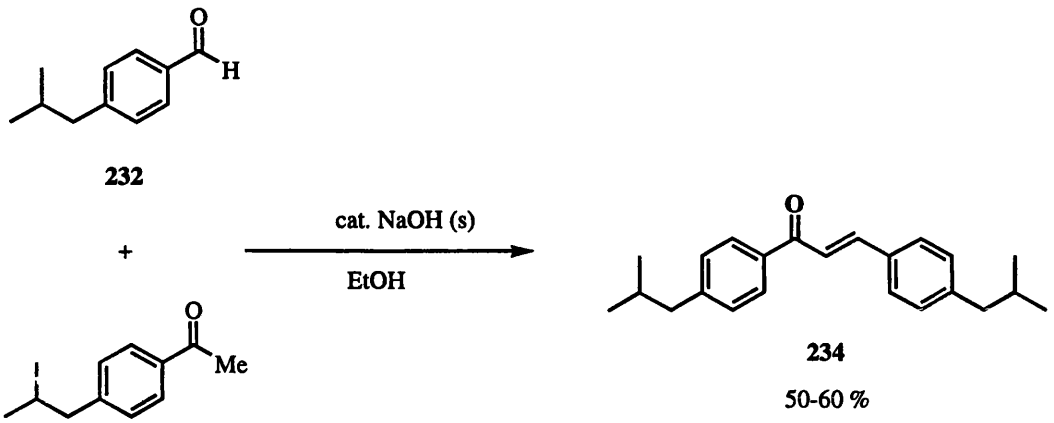
Having proven by a model study that the simple α-arylpropanoic acid, 2-phenyl propanoic acid **231** could be synthesised in just four steps from acetate **59**, in high yield and enantiomeric excess, we were now ready to apply this synthetic strategy towards the synthesis of (*S*)- Ibuprofen. **Scheme 79** depicts an outline of the synthetic plan.

The chalcone derivative **234**, was prepared *via* the Claisen-Schmidt condensation reaction, by the reaction of 4-isobutylbenzaldehyde and 4-isobutylacetophenone. We adopted a procedure developed by Murphy[220] for the preparation of chalcone derivatives whereby the reaction is carried out in EtOH, which encourages the product to precipitate from solution once it is formed. This therefore makes the work-up simple, requiring only filtration. The chalcone derivative **234** was obtained in 50-60% yield as a pale yellow solid (**Scheme 80**).

Scheme 79


O
H
232
+
Claisen-Schmidt Condensation
O
Me
233
O
234
PhO2S
SO2Ph
Asymmetric Pd-cat.
allylic substitution
OAc
239
238
ozonolysis
PhO2S
SO2Ph
OH
240
desulfonylation
Me
OH
241
oxidation
Me
CO2H
197
Ibuprofen

Scheme 80



The structure was determined *via* analysis of the ^{1}H NMR spectrum. The four methyl groups of the isobutyl side chain were observed at 0.91 and 0.92 ppm. The alkene protons were observed at 7.20 and 7.27 ppm and were found to couple to one another with a coupling constant of 7.8 Hz. The presence of a conjugated carbonyl group was shown by ^{13}C NMR with a characteristic signal that appeared at 190.2 ppm. Micro-analysis also confirmed the structure to be chalcone **234**. IR spectroscopy showed the presence of an absorption at 1661.3 cm^{-1} corresponding to C=O stretch (compare with chalcone 1661.6 cm^{-1}) and C=C stretch to be at 1596.6 cm^{-1} (compared to commercially available chalcone 1604.6 cm^{-1}).

The Luche reduction of this compound, (*2E*)-1,3-*bis*(4-isobutylphenyl)-2-propen-1-one **234**, with sodium borohydride and cerium trichloride formed the corresponding alcohol, **235**, in 94% yield (**Scheme 81**). The alcohol was identified using analysis of IR spectra, which showed the disappearance of the carbonyl signal and the appearance of an OH stretch at 3356 cm^{-1}, along with analysis of ^{1}H NMR spectra which showed a broad singlet at 2.03 ppm as well as a doublet appearing at 5.33 ppm corresponding to C<u>H</u>OH.

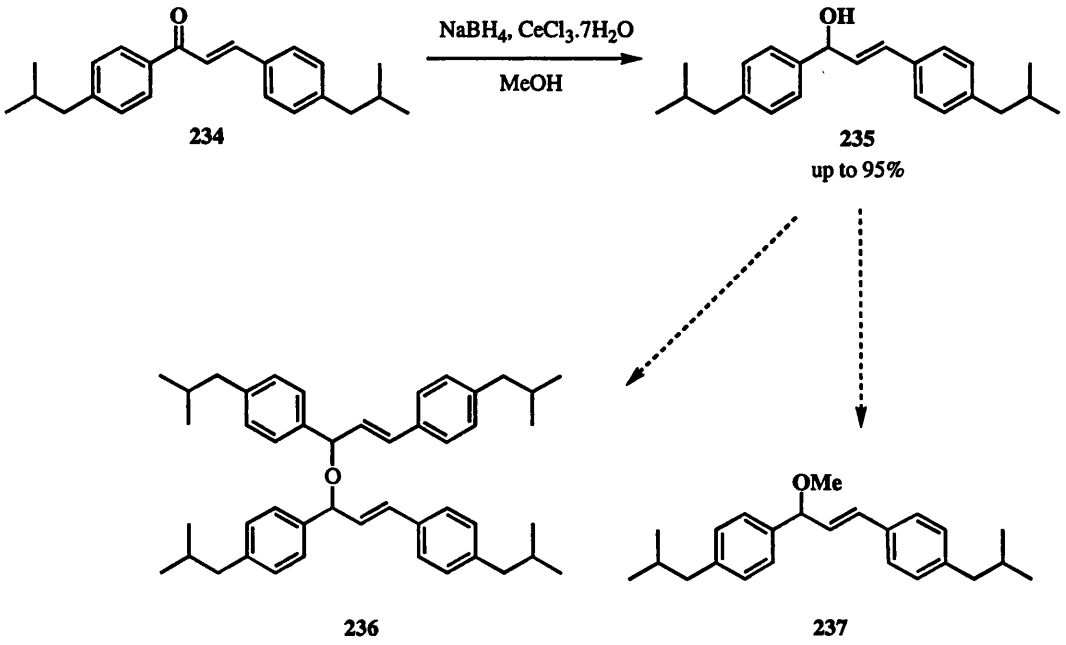
The reaction can be followed by tlc, which shows the formation of the alcohol spot below the chalcone spot.

This reaction produced a number of impurities. A compound was sometimes observed which had an R_f higher than the starting material, therefore appeared above the alcohol spot by tlc. This compound could be separated from the desired product by flash column chromatography. Analysis of the ^1H NMR showed the presence of a doublet at 4.75 ppm (downfield to CHOH) corresponding to C<u>H</u>OX, which was coupled to an alkene proton. The presence of a singlet peak at 3.36 ppm, which integrated to three protons, suggested that this unknown compound could the methyl ether **237**.

Another impurity was also evident by the presence of a signal below the C<u>H</u>OH signal of the alcohol. Two doublets (or a doublet of a doublet) were found between 5.05 and 5.09 ppm, with coupling constants of 7.0 and 7.1 Hz. This compound also gave signals at the alkene region, between 6.21 ppm and 6.39 ppm and a doublet at 6.56 ppm (J=15.8 Hz) corresponding to C<u>H</u>=CHX. All the other peaks on ^1H NMR exactly matched those of the alcohol. The fact that the ^1H NMR of this compound was very similar to that of the alcohol and with the slight difference in the chemical shift of the proton C<u>H</u>OX carbon and that this appeared to be two doublets almost superimposed with one another suggested to us that this compound could be the dimerised alcohol **236** (**Scheme 81**).

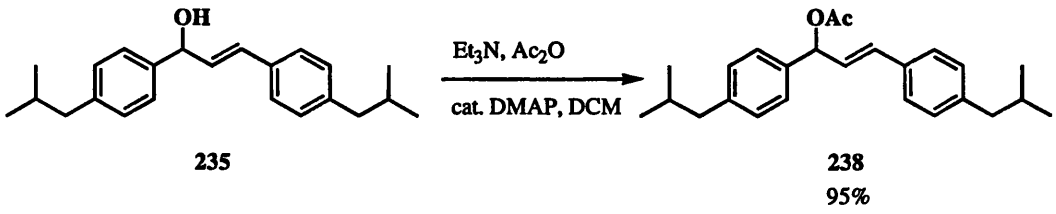
Hence the reaction was worked up and the product taken forward to the next step as soon as the starting material was consumed in order to avoid dimerisation of the alcohol. Alcohol **235** was therefore used in the next step as soon as it was formed. Neither of the impurities, the methyl ether **237** or the dimer **236** could be used as the precursors of acetate **238**.

Scheme 81



Acetylation of alcohol (2*E*)-1,3-*bis*(4-isobutylphenyl)-2-propen-1-ol **235** using acetic anhydride, trietylamine along with a catalytic amount of DMAP formed the acetate in 95% yield (**Scheme 82**).

Scheme 82

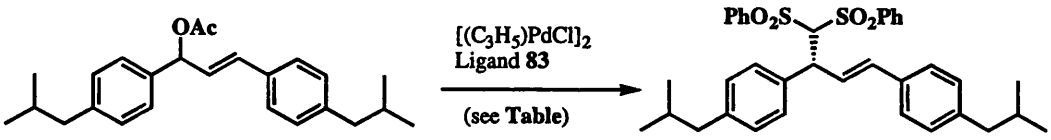


Inspection of ^{1}H NMR spectrum revealed the disappearance of the doublet at 5.33 ppm and the appearance of a doublet at 6.41 ppm corresponding to CH=CHCHOAc. The acetate signal was observed at 2.11 ppm. ^{13}C NMR showed the characteristic carbonyl peak at 170.1 ppm. The stage was now set for the palladium catalysed allylic substitution reaction.

The palladium catalysed reaction of racemic acetate **238** with sodium diphenylsulfonyl methane, under the reaction conditions outlined in **Table 3** (entry 2), led to the formation of the substitution product in 96% yield and 79% e.e., which was obtained as a colourless crystalline solid (**Scheme 83**). The product (**239**) was analysed using ^{1}H NMR which identified a doublet at 5.08 ppm corresponding to C<u>H</u>$(SO_2Ph)_2$ which was coupled to CH=CHC<u>H</u> with a coupling constant of 2.4 Hz. The structure was also confirmed *via* mass spectroscopy as well as micro-analysis.

The results obtained from the allylic substitution reaction are shown in **Table 3**. We were pleased to obtain a higher yield for this reaction than we did for the allylic substitution step in the 'model study'. Reducing the ligand loading from 6% to 5% reduced the yield by 36% and the enantiomeric excess by 3%.

Scheme 83



238 **239**

Table 3. Asymmetric palladium catalysed allylic substitution on substrate **238.**

	Conditions	Yield (%)	ee (%)
Entry 1	1.25 mol% $[(C_3H_5)PdCl]_2$ 5 mol% Ligand **83** $NaCH(SO_2Ph)_2$ 70 °C	60	76
Entry 2	1.5 mol% $[(C_3H_5)PdCl]_2$ 6 mol% Ligand **83** $NaCH(SO_2Ph)_2$ 70 °C	96	79
Entry 3	1.5 mol% $[(C_3H_5)PdCl]_2$ 6 mol% dppe $NaCH(SO_2Ph)_2$ 70 °C	90	-

The asymmetric reaction was also carried out on a larger scale of 4.0 g using the same conditions as in entry 2. A yield of 93% and an ee of 79% were obtained from this reaction illustrating that it was possible to scale up.

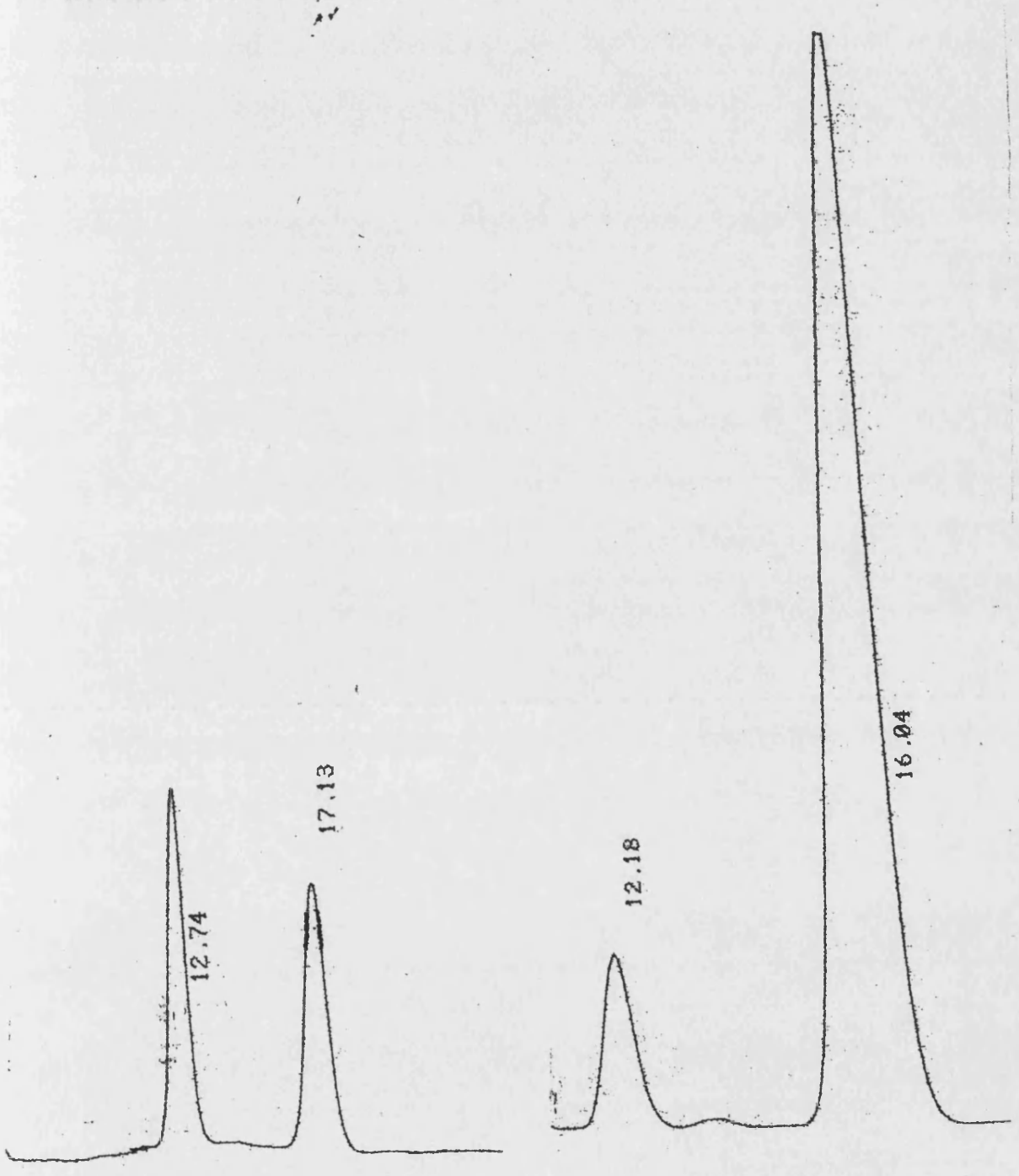
We also prepared racemic **238** employing dppe as the ligand. This reaction formed the substituted allylic sulfone **239** in 90% isolated yield. This was then used in HPLC analysis to identify the peaks corresponding to the two different enantiomers of **239**. The enantiomeric excess of the product was therefore determined *via* HPLC analysis, using a chiral AD column.

HPLC analysis of compound (±)-**239** and (*S*)- **239**

chiral AD column

70:30 Hexane/ IPA

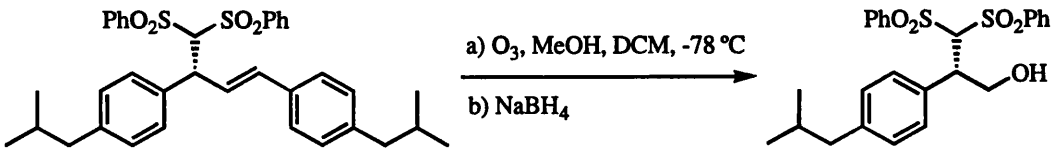
1mL/ min.



Once again, both the asymmetric and the racemic synthesis of the target molecule were carried out side by side for ee determination purposes.

As in the model study, ozonolysis followed by a reductive work-up led to the cleavage of the C=C bond in compound **239**. The reaction was quenched with $NaBH_4$ once the colour of the solution turned blue, indicating ozone saturation, and once there was no more starting material left as judged by tlc. The desired product, 2-(4-isobutyl)-3,3-*bis*(phenylsulfonyl)-1-propanol, **240**, was formed in 83% yield as a colourless solid (**Scheme 84**). The presence of two sulfone groups as well as an alcohol functionality meant that this compound was very polar. It was purified by flash column chromatography using 20% EtOAc/ PE to elute the impurities followed by pure MeOH to elute the product off the column. The structure was elucidated using ^1H NMR analysis, which revealed the disappearance of the allylic protons at 6.17 and 6.81 ppm. Instead it indicated the appearance of two doublet of doublets at 4.29 and 4.40 ppm corresponding to the diastereotopic protons $C\underline{H_2}OH$. The structure was also confirmed by micro-analysis.

Scheme 84



239
79% ee

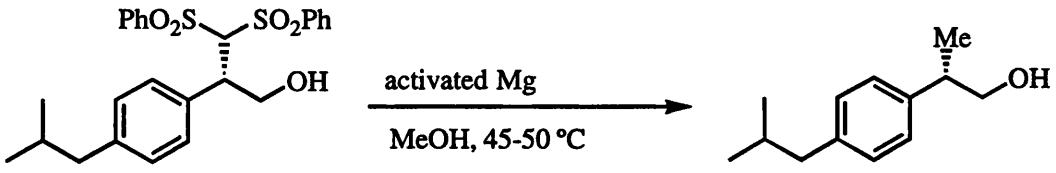
240
83%
79% ee

This alcohol was in turn desulfonylated, using the same method as in the model study, employing Mg in methanol (**Scheme 85**). ^1H NMR showed 100% conversion of starting material. The product was also pure judged by ^1H NMR and

therefore did not require further purification. The structure was analysed by ^1H NMR spectroscopy which showed the disappearance of the doublet at 5.12 ppm corresponding to C<u>H</u>$(SO_2Ph)_2$ as well as the doublet of doublet of doublet at 4.06 ppm corresponding to C<u>H</u>CH$(SO_2Ph)_2$ proton of the starting material **240**.

The methyl protons of **240** were observed as a doublet at 1.26 ppm. These data were also compared to that of literature values,[221] which indicated the structure to be correct.

Scheme 85

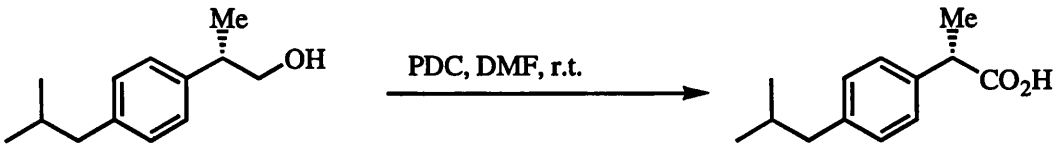


240
79% ee

241
100% conversion
by ^1H NMR
79% ee

Oxidation of the primary alcohol **241**, with PDC in DMF led to the formation of (*S*)-Ibuprofen in 88% yield and 79% e.e. (**Scheme 86**). The enantiomeric excess of Ibuprofen was determined using HPLC analysis.

Scheme 86



241
79% ee

197 (*S*)-IBUPROFEN
88%
79% ee

It is worth mentioning here that there are a number of reports in literature, which describe the oxidation of alcohol **241** to Ibuprofen (**197**). For example, $KMnO_4$

along with H_2SO_4 has been used to obtain Ibuprofen in 76% yield,[222] whereas CrO_3 and H_2SO_4 has been reported[223] to form Ibuprofen in 54% yield. However the highest yield obtained for this reaction seems to be by Kiyoura[224] who has reported the oxidation of racemic **241** to racemic Ibuprofen in 92% yield, using catalytic Pd/ C and O_2 in an aq. NaOH medium.

We were once again pleased to discover that asymmetry was successfully introduced into the molecule and that no epimerisation of the chiral centre was observed in any of the consecutive synthetic steps.

In summary we have demonstrated that enantiomerically enriched Ibuprofen can be prepared in high yield and good e.e. using asymmetric palladium catalysed allylic substitution as the key step of the synthesis.

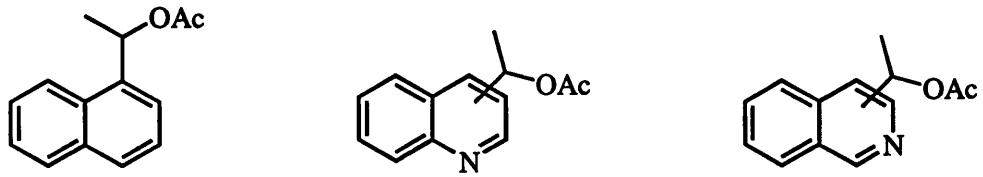
2.5 Asymmetric Synthesis of Naproxen

Having made enantiomerically enriched 2-phenylpropanoic acid **231** and Ibuprofen **197** *via* enantioselective palladium catalysed allylic substitution, as discussed; we turned our attention towards the synthesis of (*S*)-Naproxen **198**.

Naproxen is another member of the α-aryl propanoic acids, which exhibits anti-inflammatory and analgesic properties. Like Ibuprofen, it is the (*S*)-enantiomer of Naproxen that is the pharmaceutically active form.

Although there are no examples in literature of the use of palladium catalysed allylic substitution reaction for the synthesis of Naproxen, recently naphthylmethyl acetates and even their quinoline and isoquinoline analogues have been investigated as substrates[225] for the allylic substitution reaction (**Scheme 87**). It was observed that the relative positions of the nitrogen and the acetoxymethyl substituent were crucial in terms of their reactivity, some combinations being completely unreactive. This chemistry could also be modified and used towards Naproxen synthesis.

Scheme 87

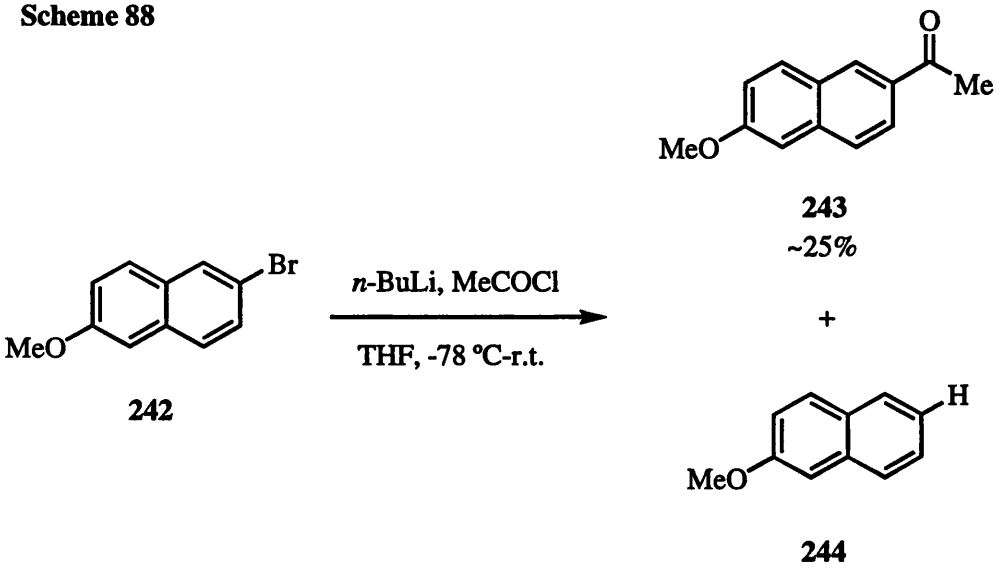


We conceived that the synthesis of (*S*)-Naproxen could be achieved using the methodology described in **Chapters 2.2** and **2.3**, through palladium catalysed asymmetric allylic substitution on acetate **251**.

The chalcone derivative **247** was prepared from aldehyde **245** and ketone **243** in high yield via a Claisen-Schmidt condensation reaction.

Initial attempts to prepare ketone **243** in one step, from 2-bromo-6-methoxy naphthalene **242**, by carrying out lithium halogen exchange reaction with BuLi, followed by reacting the lithiated aryl species directly with acetyl chloride failed to form the desired product in high yield. Compound **244** was also isolated from this reaction indicating that not all of the lithiated starting material had reacted with the electrophile (**Scheme 88**).

Scheme 88



242

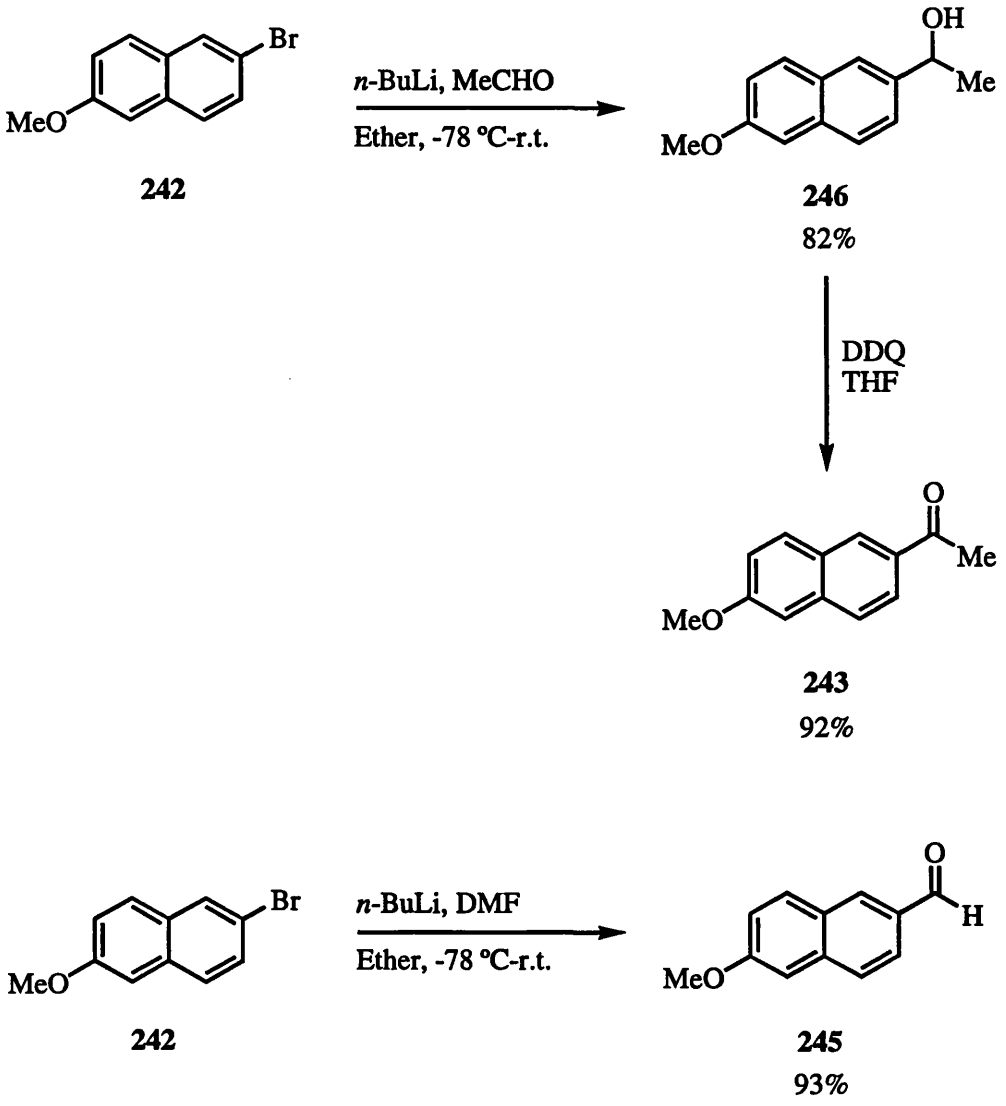
243
~25%

+

244

The precursors to the chalcone derivative **247**, aldehyde **245** and ketone **243**, were therefore conveniently synthesised by an alternative route. Both compounds were prepared on a multi-gram scale using literature procedures,[226] starting from the same inexpensive starting material, 2-bromo-6-methoxy naphthalene **242** (**Scheme 89**). The reaction of 2-bromo-6-methoxy naphthalene **242** with BuLi leads to the formation of a lithiated methoxy naphthalene species. This species reacts with DMF to form aldehyde **245**. On the other hand the reaction of the same lithiated methoxy naphthalene species with acetaldehyde leads to the formation of secondary alcohol **246**, which is the precursor for ketone **243**. Oxidation of **246** with DDQ forms ketone **243** in 92% yield (**Scheme 89**).

Scheme 89



242 → **246** (82%) → **243** (92%)

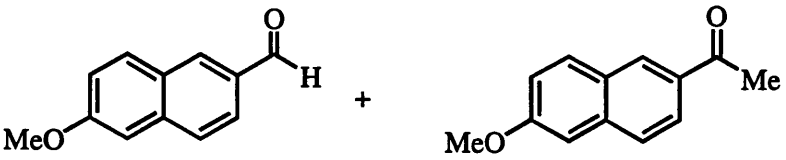
242 → **245** (93%)

(2*E*)-1,3,-*bis*(6-Methoxy-2-naphthyl)-2-propen-1-one **251** was prepared *via* the Claisen-Schmidt condensation reaction in 96% yield as a pale yellow powder, as depicted in **Scheme 90**. The structure was identified using ^{1}H NMR, which showed the disappearance of the aldehyde peak of starting material **245**, at 10.13 ppm as well as the methyl peak of the other starting material **243** at 2.71 ppm. This accompanied the appearance of a singlet at 3.94 ppm and 3.96 ppm corresponding to the methoxide protons. The alkene protons were observed together with three of the aromatic protons between 7.15 and 7.25 ppm. Analysis of mass spectra also showed the accurate mass to be correct at 368.1410. One of

the problems with this compound was that it was extremely insoluble in almost all solvents. This therefore required a large amount of methanol to be added for the Luche reduction step. Addition of other solvents such as acetonitrile into the reaction somewhat reduced the effectiveness of the reaction. We carried out the reaction in a 50:50 mixture of MeOH and DCM, but nevertheless the volume of solvent required rendered the reaction difficult to carry out.

The alcohol **248** was formed in 84% yield as a yellow powder which also was very insoluble (**Scheme 90**). The formation of the dimer and the methyl ether were sometimes observed (**Scheme 91**). The dimer **249** and alcohol **248** were separable by tlc plate using 50% ether/ petroleum ether as the solvent whereas the alcohol and methyl ether **250** were separable using 40% Ethyl acetate/ petroleum ether as the eluent.

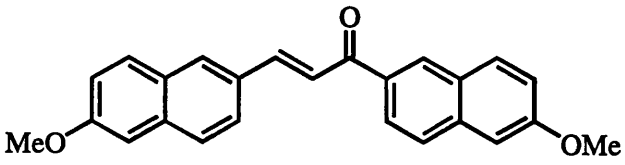
Scheme 90



245 **243**

cat. NaOH(s)

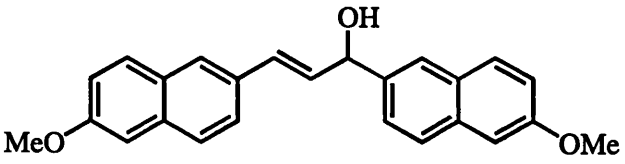
EtOH



247

96%

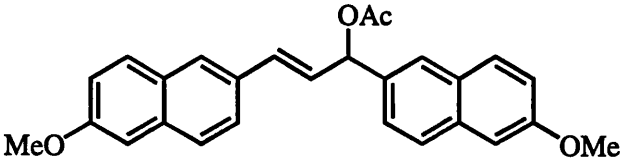
$NaBH_4$
$CeCl_3.7H_2O$
MeOH



248

84%

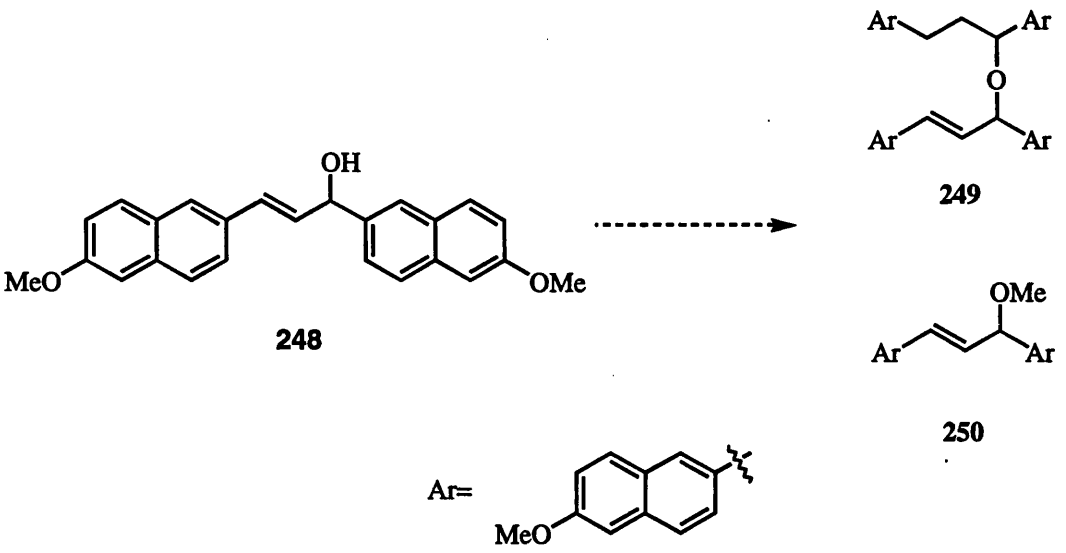
Ac_2O, Et_3N
DMAP, DCM



251

100% conversion
by ^{1}HNMR

Scheme 91



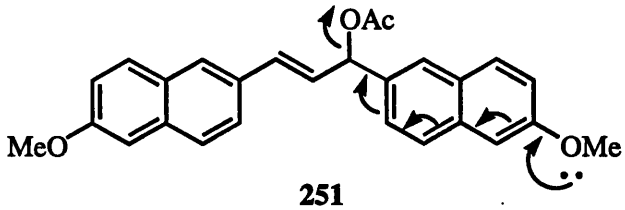
At first, many attempts to acetylate this alcohol seemed to fail. Apart from the usual acetic anhydride and triethylamine method, we also used a number of other reagents for this interconversion. These include the use of pivalic anhydride instead of acetic anhydride; pyridine along with acetyl chloride; as well as acetylimidazole which should serve both as a base and the acetate source. However analysis of ^{1}H NMR showed none or only traces of the acetate or the pivalate. We believe one of the reasons for this to be dimerisation of the alcohol in solution as evidenced by the appearance of a spot above the alcohol and above the expected acetate spots on tlc plate.

However, after repetitive reactions it was found that when a ^{1}H NMR is carried out on the product immediately after the reaction, analysis show quantitative conversion of starting material. The structure was elucidated by the presence of the characteristic acetate peak at 2.17 ppm. In addition the doublet corresponding to C<u>H</u>OH observed at 5.75 ppm had disappeared and a doublet had appeared at 6.62 ppm corresponding to C<u>H</u>OAc. Information obtained from ^{13}C NMR spectroscopy also supported this structure. We have therefore demonstrated that the products of this reaction (both the acetate and pivalate) are very unstable and

that they revert back to the starting material alcohol very rapidly on standing. Also the same result is observed when the products are dried over magnesium sulfate rather than sodium sulfate, showing that the products are also acid sensitive.

We believe that although the acetate forms, it decomposes easily due to the strongly electron donating methoxynaphthalene groups (**Scheme 92**).

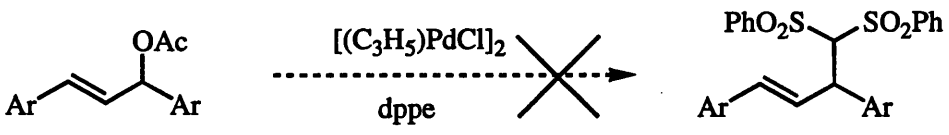
Scheme 92



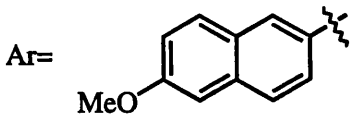
251

Unfortunately, attempts to carry out the palladium catalysed allylic substitution reaction on this substrate were unsuccessful. ^{1}H NMR shows several peaks implying decomposition of the materials. This might very well be because of the unstable nature of the acetate (**Scheme 93**).

Scheme 93



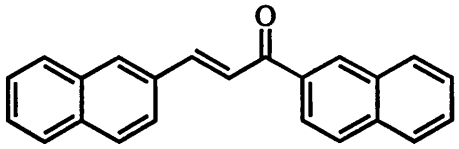
251 **252**



We were intrigued to find out whether the problem originated from the presence of the methoxy groups on the naphthalene ring. We therefore prepared chalcone derivative **253**, which lacks the methoxy groups on the 4- position. This

compound was prepared *via* the Claisen Schmidt condensation reaction starting from the commercially available 2-naphthaldehyde and 2-acetonapthone in 98% yield as a yellow powder. Unfortunately this compound revealed similar characteristics to that of chalcone derivative **247** in that it was also extremely insoluble in solvents ranging from DMSO to toluene and chloroform.

Scheme 94

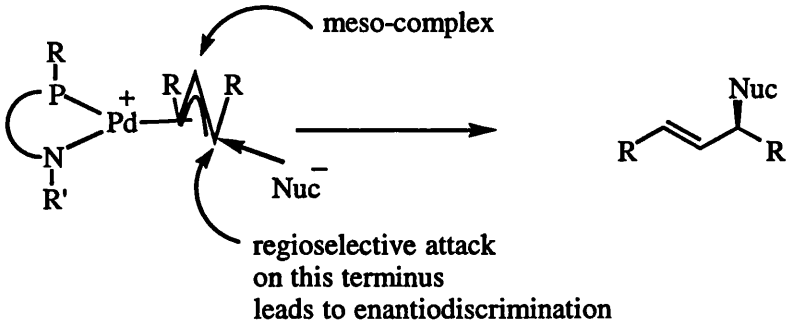


253

2.6 Atom Economy

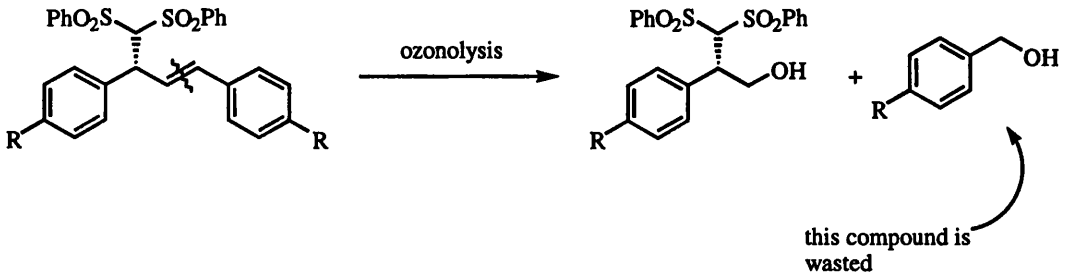
In our synthesis of α-arylpropanoic acids, we chose to use 1,3-disubstituted substrates, which form an η^3-allylic intermediate with a C_{2h} symmetry, when bound to the metal centre. This meant that the two R groups on 1 and 3 positions of the allyl moiety had to be identical in order for the two termini to be enantiotopic. Enantioselectivity can then be achieved with this *meso* type complex by controlling the regiochemistry by using the appropriate enantiomerically pure ligands (**Scheme 95**).

Scheme 95



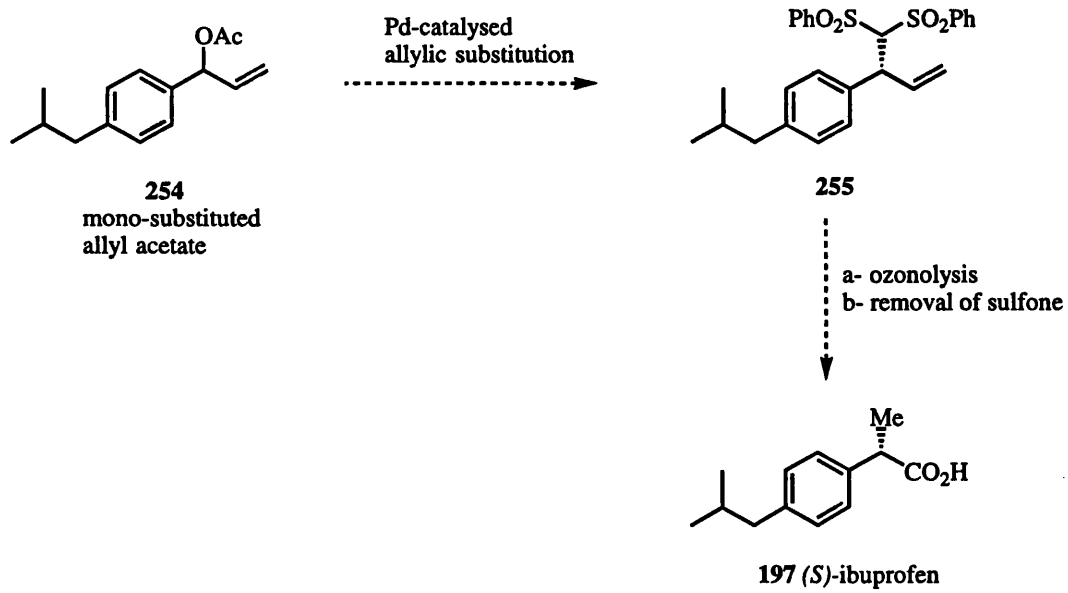
However, it can be argued that, one of the problems with the synthetic approach described in **Chapter 2** is that, once the enantioselectivity is achieved in the palladium catalysed allylic substitution step, the molecule had to be cleaved in the oxidative cleavage step, meaning that the other half of the molecule was wasted (**Scheme 96**).

Scheme 96



A more 'atom economical' approach for the synthesis of Ibuprofen would therefore be to start with the mono-substituted allyl acetate **254**. Once the substituted compound **255** is formed, simple ozonolysis and reduction of the sulfone groups would lead to asymmetric Ibuprofen (**Scheme 97**).

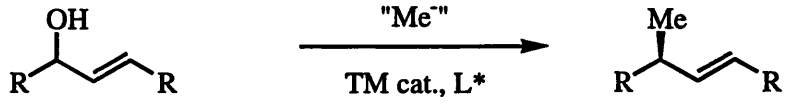
Scheme 97



This mono-substituted allylic acetate however, would lead to an unsymmetrical π-allyl species, which would mean that regiocontrol becomes an issue and enantioselectivity cannot be controlled by the same methods as used for a symmetrical *meso* system. We have tried to tackle this problem in the following chapter.

Another way in which we could achieve 'Atom Economy' would be to use a methyl synthon in the allylic substitution step. Although we have succeeded in making Ibuprofen in high yield and e.e., it would be more efficient to substitute the alcohol asymmetrically with a methyl group in one step, rather than going through the stages of acetylation of alcohol, asymmetric substitution, and desulfonylation. This might be achieved by using an organometallic nucleophile such as organo-zinc, boron, tin or copper and a transition metal catalyst such as nickel as illustrated in **Scheme 98.**

Scheme 98



Chapter 3

The Use of Tricyclohexylphosphine to Control Regioselectivity in the Palladium-catalysed Allylic Substitution Reaction

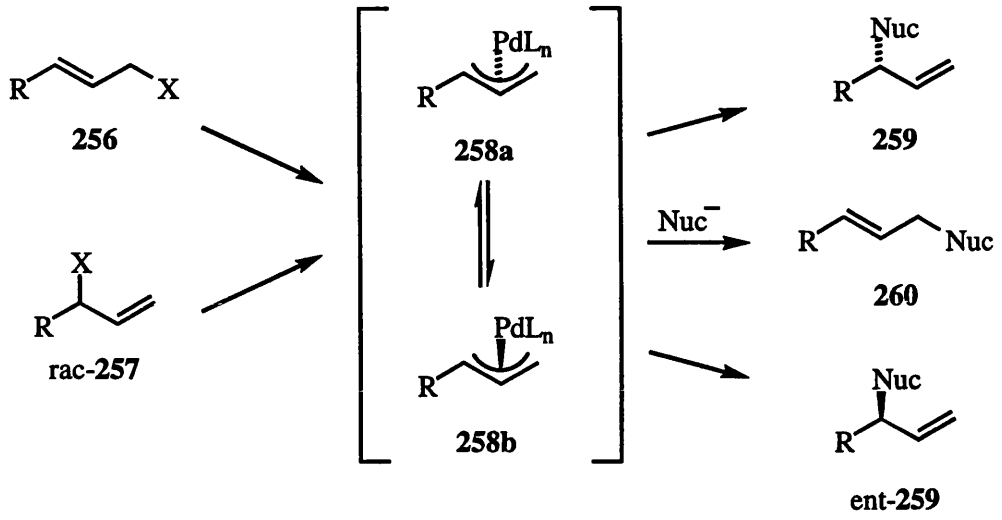
Background

As reviewed in **Chapter 1**, there are several reports in literature of chiral ligands that afford high enantioselectivities in the palladium catalysed allylic alkylation of the 1,3-diphenylallyl system **59**. This substrate is often preferred as the π-allyl moiety is C_{2h} symmetric. Hence, high enantioselectivities can be obtained as a result of preferential attack of the nucleophile at one of the enantitotopic termini. However, in cases where the allylic termini are substantially differentiated reaction results in the formation of both possible regioisomeric products.

One of the most challenging problems in allylic substitution reactions, therefore, is the lack of regiocontrol when the reaction proceeds through an unsymmetrical intermediate.

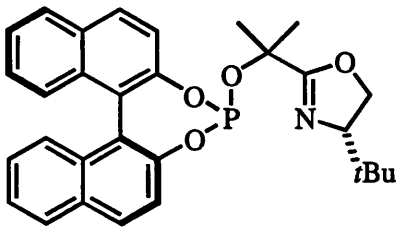
For example, monosubstituted allylic substrates such as **256** and **257** proceed through a common intermediate, **258**, which generally react predominantly at the unsubstituted allyl terminus. Consequently, irrespective of which isomer is the starting material the achiral, linear isomer **260** is formed rather than the chiral, branched product **259** or its enantiomer ent-**259**, which are the desired products for applications in asymmetric synthesis (**Scheme 99**).

Scheme 99

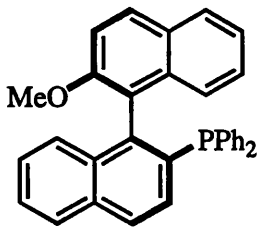


It is only recently that catalysts have been discovered which have been shown to reverse this regioselectivity. Such a reversal of regioselectivity has been achieved using palladium complexes with a few chiral ligands, although their use seems to be limited to certain substrates. For example, Pfaltz[227] has developed ligand **261**, which affords substituted products in the ratio of 76:24 in favour of the branched product, when cinnamyl acetate is alkylated using dimethyl malonate. The MeO-MOP ligand **262**, developed by Hayashi,[228] has also been reported to be regioselective in the same way (**Scheme 100**).

Scheme 100



261



262 ((*R*)-MeO-MOP)

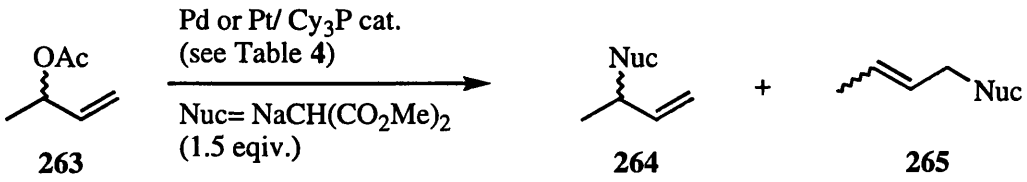
However, the most promising results have been achieved using other metal complexes such as tungsten,[182] iridium,[185] rhodium,[229] ruthenium,[230] and molybdenum.[184] These catalysts can all result in the formation of branched products under the correct reaction conditions.

Nevertheless, the search for palladium complexes that give both good regioselectivity and enantioselectivity is a major challenge since there are still large classes of substrates that give unsatisfactory results with the existing catalysts.

Use of Tricyclohexylphosphine to Control Regioselectivity

It was recently discovered within our group[231] that the Cy_3P ligand, when used in conjunction with $[(C_3H_5)PtCl]_4$ catalyses the allylic alkylation of unsymmetrical allylic acetate **263** with high regioselectivity towards the branched product **264**. Strikingly, when a palladium catalyst in combination with this ligand was tested, similar results were obtained. Whereas most ligands would favour the linear product **265**, it was found that Cy_3P was regioselective and afforded the branched product **264** (**Scheme 101** and **Table 4**).

Scheme 101



263 **264** **265**

Table 4. Allylic alkylation of But-2-enyl Acetate **263** with Sodium Dimethylmalonate [a]

Catalyst	**264/ 265**
$Cy_3P[(C_3H_5)PtCl]_4$	15.4:1
$Cy_3P/ [(C_3H_5)PdCl]_2$	16:1

[a] Results from Matthew L. Clarke [PhD Thesis, University of Bath, 1999]
[b] All reactions run using 1.5 eqiuv. of $NaCH(CO_2Me)_2$ nucleophile, THF solvent at 20 °C. In all cases conversion was 100%, as determined by GC.

The results obtained using Cy_3P as the ligand are surprising. As palladium is usually the metal of choice for allylic substitution reactions, it seemed important to study the origin of this unusual ligand effect and to explore its synthetic potential.

Initially, a study was carried out whereby Cy_3P was compared with other ligands, in terms of their regioselectivity, in the allylic alkylation of but-2-enyl acetate **263** **(Table 5)**

Table 5.[a] Effect of Ligand on Regioselectivity of Allylic Alkylation of But-2-enyl Acetete **263** with Sodium Dimethylmalonate

Ligand [b]	**264/ 265**[c]
Cy_3P	11.5: 1
Ph_3P	1: 2
$[2,4,6\text{-}(CH_3O)_3C_6H_2]_3P$	1:3.9
tri-*o*-tolylphosphine	1: 1.5
$(p\text{-}CH_3O\text{-}C_6H_4)_3P$	1: 1.2
$(p\text{-}FC_6H_4)_3P$	1: 1.3
$Cy_2PCH_2CH_2PCy_2$	1: 1.1
dppe	1:1.4

[a] Matthew L. Clarke [PhD thesis, University of Bath, 1999]
[b] All reactions run using 2.5 mol% of $[(C_3H_5)PdCl]_2$ catalyst, 1.5 eqiuv. of $NaCH(CO_2Me)_2$ nucleophile, THF solvent at 20 °C. In all cases conversion was 100%, as determined by GC.
[c] Determined by GC and ^1H NMR.

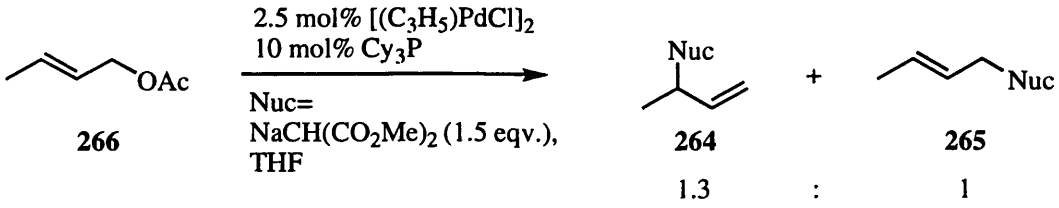
Tricyclohexylphophine is a bulky and strongly electron donating phosphine. This is quantified by its large cone angle ($\theta = 170°$)[232] and the high pKa value of its conjugate acid (pKa = 9.70). This can be compared with Ph_3P ($\theta = 145°$, pKa = 2.73).[233] The ligands in **Table 5** were chosen because they share similar characteristics with Cy_3P and can therefore be used to determine whether the regioselectivity obtained can be attributed to a certain property of the ligands. Tri (2,4,6-trimethoxy-phenyl)phosphine[234] is both more bulky and basic ($\theta = 184°$, pKa = 11.02) than Cy_3P, but gives regioselectivity opposite to that of the Cy_3P/ Pd-catalysed reactions. Tri-*o*-tolylphosphine is one of the most bulky phosphines ($\theta = 194°$, pKa = 3.08), but gives mainly linear products, contrary to the

tricyclohexylphosphine system. On the other hand, Tris(4-methoxyphenyl)- and tris(4-flourophenyl)phosphines have a similar cone angle to that of tricyclohexyphoshine (θ = 145°), but have different basicities (pKa = 4.57, and 1.97) respectively.[233]

It is therefore reasonable to conclude that there appears to be no direct relationship between the cone angle or basicity of a ligand and the proportion of branched/ linear products formed in this reaction.

It was suggested to us that the results obtained may be due to a strong "memory effect"[235] when Cy_3P was used as the ligand (the product is the same regioisomer as the starting material). To test this theory, the reactivity of regioisomeric allylic acetate **266** was examined (**Scheme 102**).

Scheme 102



266 **264** : **265**

1.3 : 1

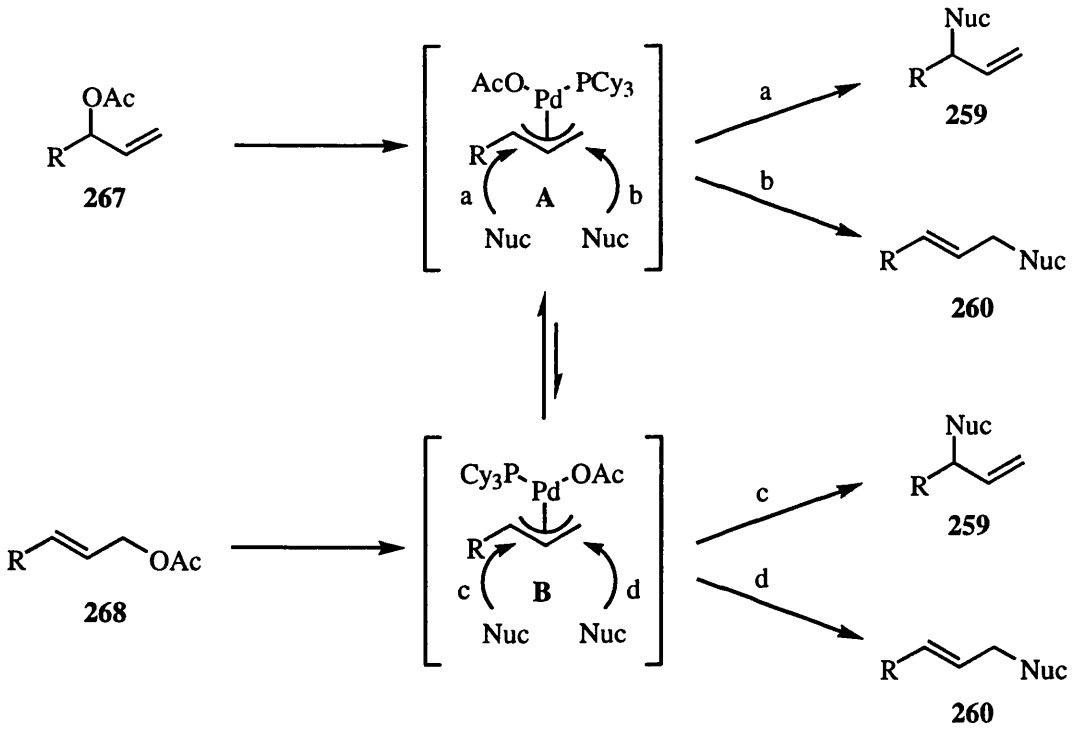
The regioselectivity was altered from 16:1 to 1.3:1 i.e. much greater proportions of linear products were obtained from linear starting materials. This is good evidence that a partial memory effect is associated with this ligand.

Traditionally, the intermediate palladium allyl species 'forgets' the stereochemistry of the starting material. Hence, these early results were very exciting and showed a very novel trend, distinct from other ligands studied in this area.

At this stage, our aim was to design new systems which had good, perhaps perfect 'memory' and to elucidate the mechanism and hence the origin of this regioselectivity.

A possible mechanism has been proposed in **Scheme 103** that could account for a memory effect. Starting with the branched regioisomer, **267**, we obtain more of the branched product **259**. Staring with the linear regioisomer we obtain comparatively more linear product, **260**. One possible explanation would be if only one phosphine ligand was involved in the intermediate π-allyl complex. The leaving acetate probably resides *cis-* to the allyl terminus from which it came. The nucleophile would attack *trans-* to the phosphorus, resulting in the formation of branched product from branched starting material and similarly linear product from linear starting material.

Scheme 103-Proposed mechanism



One of the initial experiments we did to test this theory was to use only one equivalent of ligand per palladium, rather than using 2 equivalents of ligand per palladium (**Table 6**).

Table 6. Comparison of regioselectivity: using two ligands per Pd and one ligand per Pd.

Catalyst	**264** : **265**[b]	Conversion
2.5 mol% $[(C_3H_5)PdCl]_2$ 10 mol% Cy_3P	16 : 1	100%
2.5 mol% $[(C_3H_5)PdCl]_2$ 5 mol% Cy_3P	16 : 1	100%

[a] All reactions run using 1.5 eqiuv. of $NaCH(CO_2Me)_2$ nucleophile, THF solvent at 20 °C. In all cases conversion was 100%, as determined by GC.
[b] Determined by GC and confirmed by ^1H NMR.

This experiment showed that regioselectivity does not change whether one or two equivalents of Cy_3P per palladium is used, suggesting that indeed only one ligand might be associated with palladium in the π-allyl intermediate. However, the addition of two equivalents of ligand does not reduce selectivity either. Hence, more detailed mechanistic studies are needed.

Optimisation of Regioselectivity: can we have perfect memory?

Assuming that the mechanism we have proposed in **Scheme 103** is correct; starting from branched substrate, proceeding through 'route a', the branched product would be obtained. In the same manner, if we started from the linear regioisomer, proceeding *via* 'route d', the linear product is obtained.

Although the regioselectivity obtained thus far is good, we could improve it further if we could force the reaction to proceed through these specific routes only.

One of the experiments performed in this direction was to analyse solvent effects. The results are outlined in **Table 7.**

Table 7. Regioselective allylic alkylation of acetate **263** with dimethyl malonate: Effect of different solvents.

Substrate	Ligand	Solvent/ Conditions[a]	Products **264/ 265**[b]
263	Ph_3P	THF	1:1
263	Cy_3P	THF	16:1[f]
263	Cy_3P	Et_2O[d]	16:1
263	Cy_3P	CH_2Cl_2	120:1[e]
263	Cy_3P	Toluene	40:1
263	Cy_3P	Hexane[c]	9:1

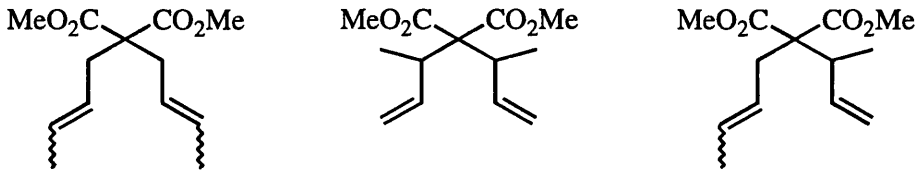
[a] All reactions run using 2.5 mol% of $[(C_3H_5)PdCl]_2$ catalyst and 10 mol% ligand, 1.5 eqiuv. of $NaCH(CO_2Me)_2$ nucleophile. Reactions were carried out at r.t. except in the cases noted.
[b] Determined by GC.
[c] Heated at 65°C (Pd not soluble in this solvent at r.t.)
[d] Heated at reflux (Ligand not soluble at r.t. in this solvent)
[e] 9% disubstitution product isolated (from 18% starting material).
[f] 10-12% disubstitution product isolated.

We were pleased to find that branched substrate **263** undergoes palladium catalysed allylic substitution with $NaCH(CO_2Me)_2$ to provide the branched substitution product **264** with up to 120:1 regioselectivity when dichloromethane is employed as the solvent.[236] It is unclear why dichloromethane should provide higher regioselectivity than either THF or Toluene, but the nucleophile is only sparingly soluble in this solvent. However, it is worth noting that the reaction

proceeds much faster in DCM, than it does in THF. This might provide an explanation for the higher selectivity. If it is the case that the nucleophile attacks the π-allyl intermediate **A** faster in DCM than in the other solvents, this would allow less time for **A** and **B** to equilibrate and the reaction would proceed through paths a / b rather than c / d (see **Scheme 103**).

On some occasions, a small by-product could be detected by TLC. It was easily isolated by flash column chromatography and was characterised to be a mixture of the diallylated compounds (**Scheme 104**).

Scheme 104

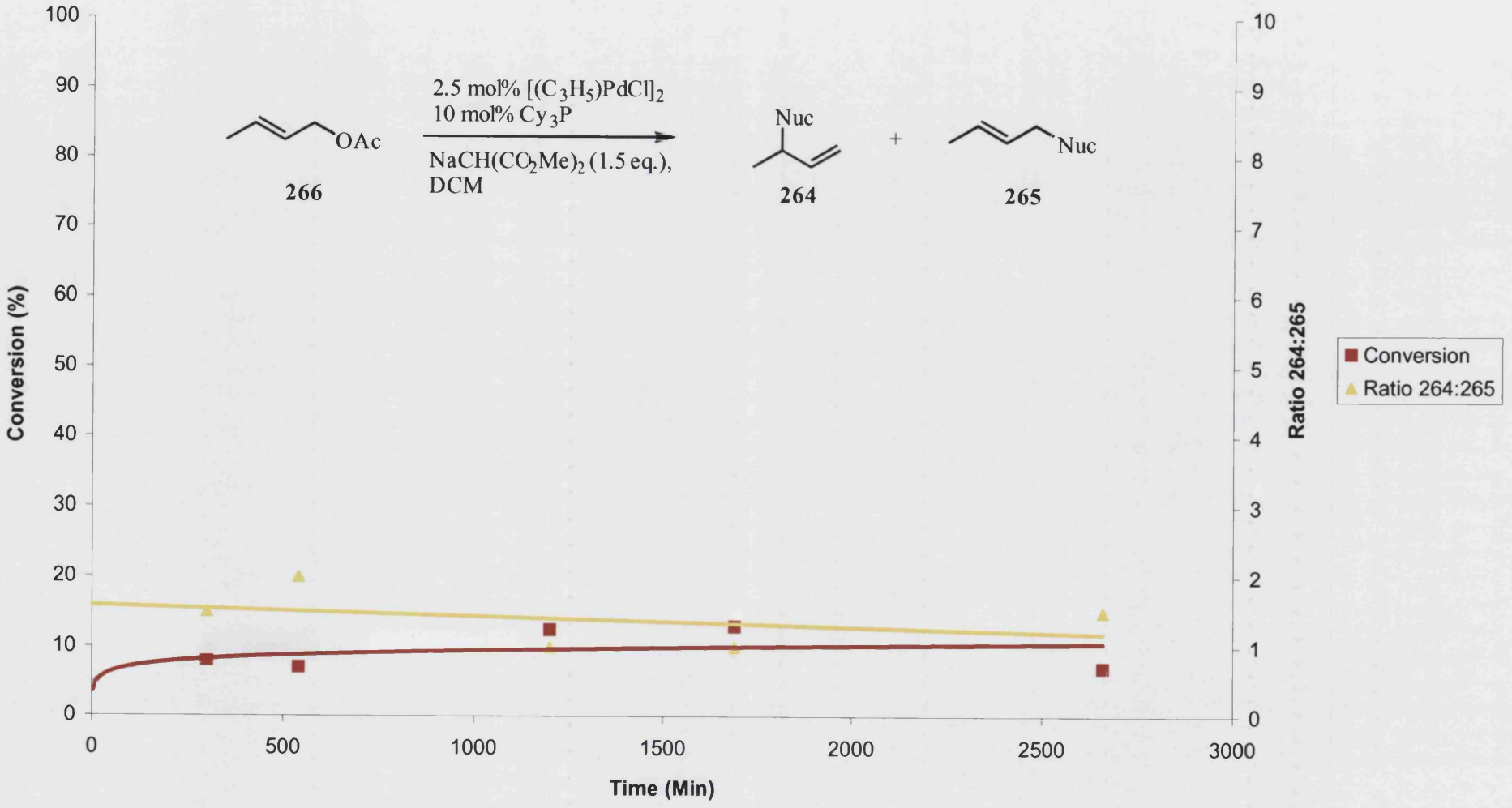


This result (Entry 4, **Table 7**) urged us to carry out the reaction on the corresponding linear acetate **266** in DCM. We found that the linear acetate does not give the same ratio of product isomers, affording little regioselectivity, and also is a very sluggish reaction partner when dichloromethane is employed as the solvent (although in THF, the reaction goes to completion in 7h with the same distribution of regioisomers) (**Table 8**).

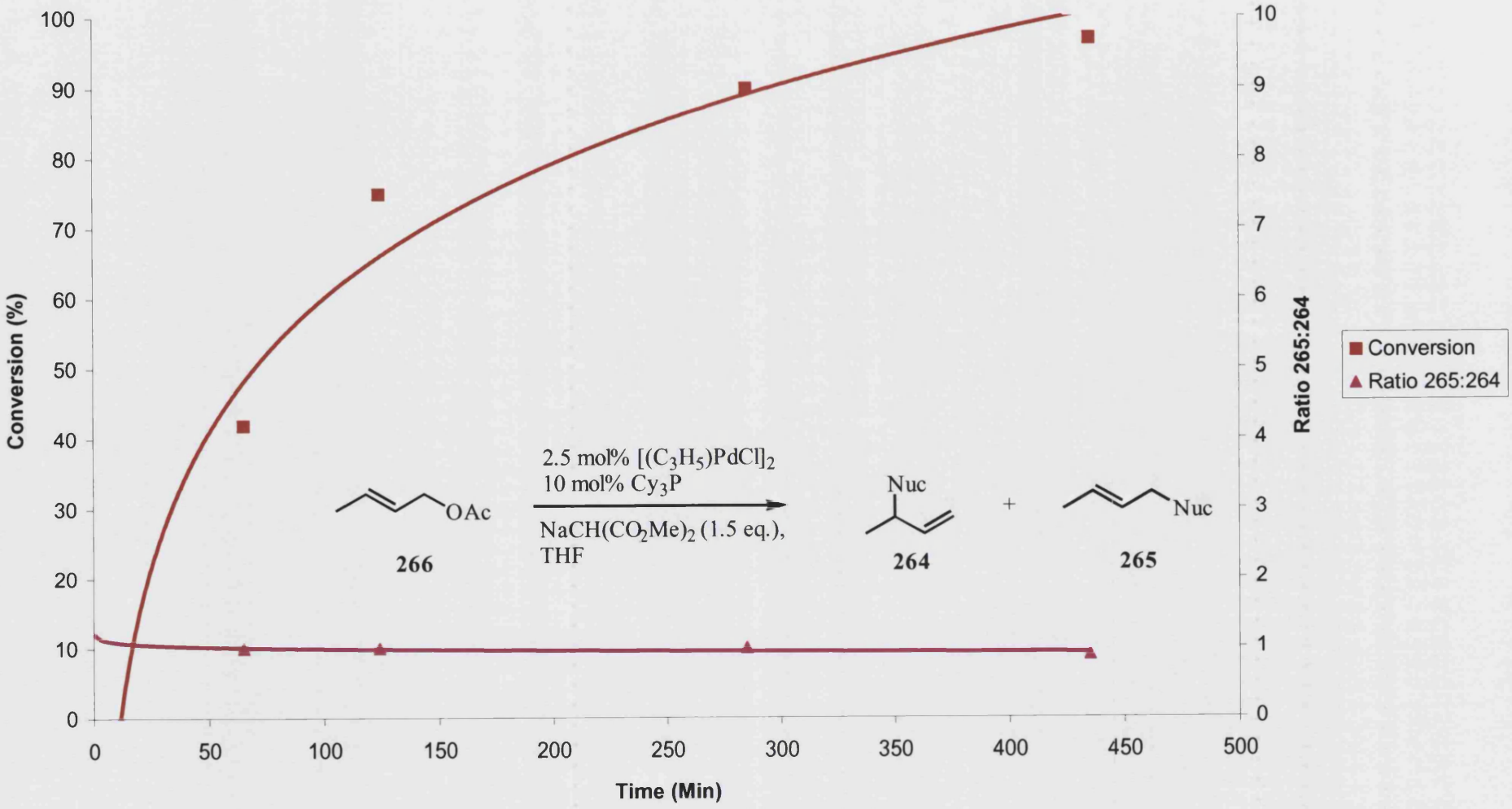
Graphs 1 and **2** illustrate the conversion of linear acetate **266** against time in DCM and THF respectively. The change in the branched to linear product ratio (**264**:**265**) against time is also illustrated.

The low conversion of the linear acetate in DCM is notable and encouraged us to perform a competition reaction between the linear and branched acetates.

Graph 1-Reaction of linear acetate 266 with dimethyl malonate



Graph 2-Reaction of linear acetate 266 with dimethyl malonate



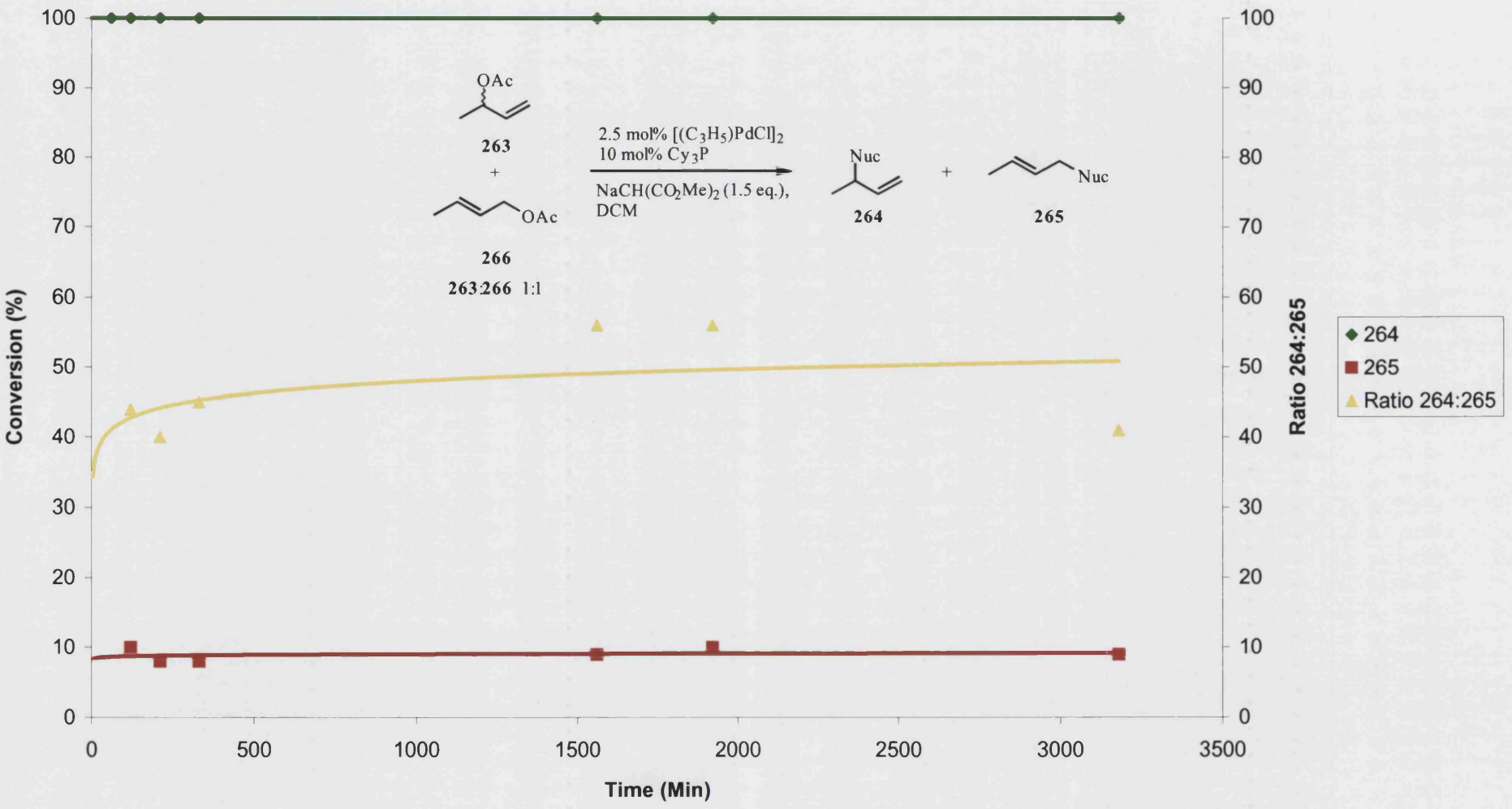
A 1:1 mixture of branched acetate **263** and linear acetate **266** was subjected to palladium catalysed allylic substitution with $NaCH(CO_2Me)_2$ using tricyclohexylphosphine as the ligand. After 1 hour, analysis of the reaction mixture revealed that all of the branched acetate had been consumed, and the ratio of branched to linear substitution products was 44:1 (**264**:**265**). Even after 50 hours, only 10% of the linear acetate had reacted, demonstrating a very considerable preference for the branched substrate over the linear acetate (**Graph 3**). Interestingly, when triphenylphosphine is used as the ligand, the linear acetate reacts to completion in less than 1 hour (**Table 8**). It seems reasonable to assume that the bulky palladium/ tricyclohexylphosphine combination has steric preference for the less substituted alkene.

Table 8. Reaction of Linear Acetate **266** with Sodium Dimethylmalonate

Ligand [a]	Solvent	**264** : **265** [b]	Time (h.)
Ph_3P	THF	1 : 1.3	1
Cy_3P	THF	1.3 : 1	7
Cy_3P	DCM	1 : 1	50 [c]

[a] Reactions were run using 2.5 mol% of $[(C_3H_5)PdCl]_2$ catalyst, 10 mol% ligand, and 1.5 equiv. of NaCH (CO2Me) 2 at r.t. Conversion was 100%, as determined by GC, except otherwise stated.
[b] Determined by GC and checked by ^1H NMR.
[c] The reaction proceeded to 10% conversion after 50 h.

Graph 3-Competition Reaction between linear acetate 266 and branched acetate 263



Effect of Counterion on Regioselectivity

The nature of the nucleophile can have an important impact on the mechanistic aspect of the reaction. In this respect one of the conditions to be considered is the counterion of the nucleophile. This can have a crucial impact on the properties of the nucleophile. For example, counterions could change the relative rate of nucleophilic addition depending on their effective steric size, which is a function of the tightness of the ion pair. The counterion could also affect the properties of the nucleophile by making it more or less soluble.

We therefore tested a number of counterions. The results are outlined in **Table 9.**

Table 9. Effect of the nucleophile counterion in the palladium catalysed allylic substitution of **263** with dimethyl malonate.

Entry	Base	Additive	Solvent	**264/265**[b]	Time (h.)	Conversion[b] (%)
1	NaH	n/a	DCM	120:1	<1	100
2	BSA	KOAc	DCM	19:1	55	18/ 1
3	DBU	n/a	DCM	23:1	51	1/ 4
4	NaH	15-crown-5	DCM	188:1	48	1/ 1.6
5	NaH	n/a	THF	16:1	1	100
6	KH	n/a	THF	23:1	1.5	100

[a] Reactions were run at r.t. using 2.5 mol% of $[(C_3H_5)PdCl]_2$ catalyst, 10 mol% Cy_3P ligand, and 1.5 equiv. of CH2 (CO2Me) 2, 1.1 equiv. (to malonate) of base.
[b] Determined by GC.

This data indicates that compared to the reaction of NaH and dimethylmalonate in DCM (entry 1) which takes less than 1 hour to reach completion, the reactions of BSA and DBU seem to take a much longer period of time (entries 2 and 3 respectively). Especially in the case of DBU even after 55 hours only about 20%

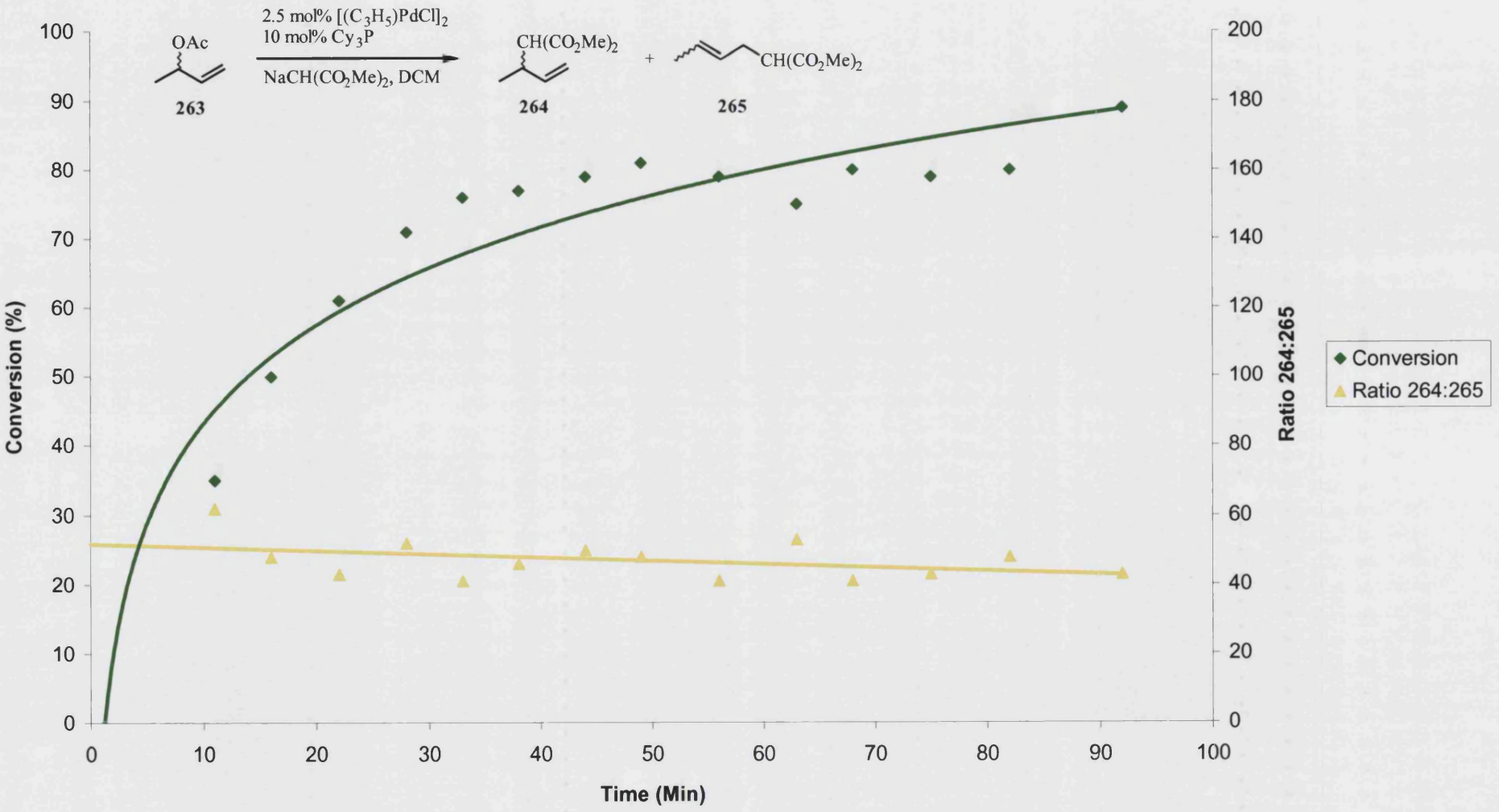
product is obtained. Both bases BSA and DBU seem to give comparatively lower selectivity than the corresponding reaction of NaH, although they are still highly regioselective. It is only in the case where 15-crown-5 is used along with NaH that higher selectivity than with the NaH reaction itself is obtained.

On the other hand compared to the reaction of NaH in THF, the corresponding reaction of KH as base seems to give higher selectivity. It is worth noting that no disubstitution product was observed for this reaction. Therefore the high regioselectivity could not be due to 'Kinetic Discrimination' induced by disubstitution.

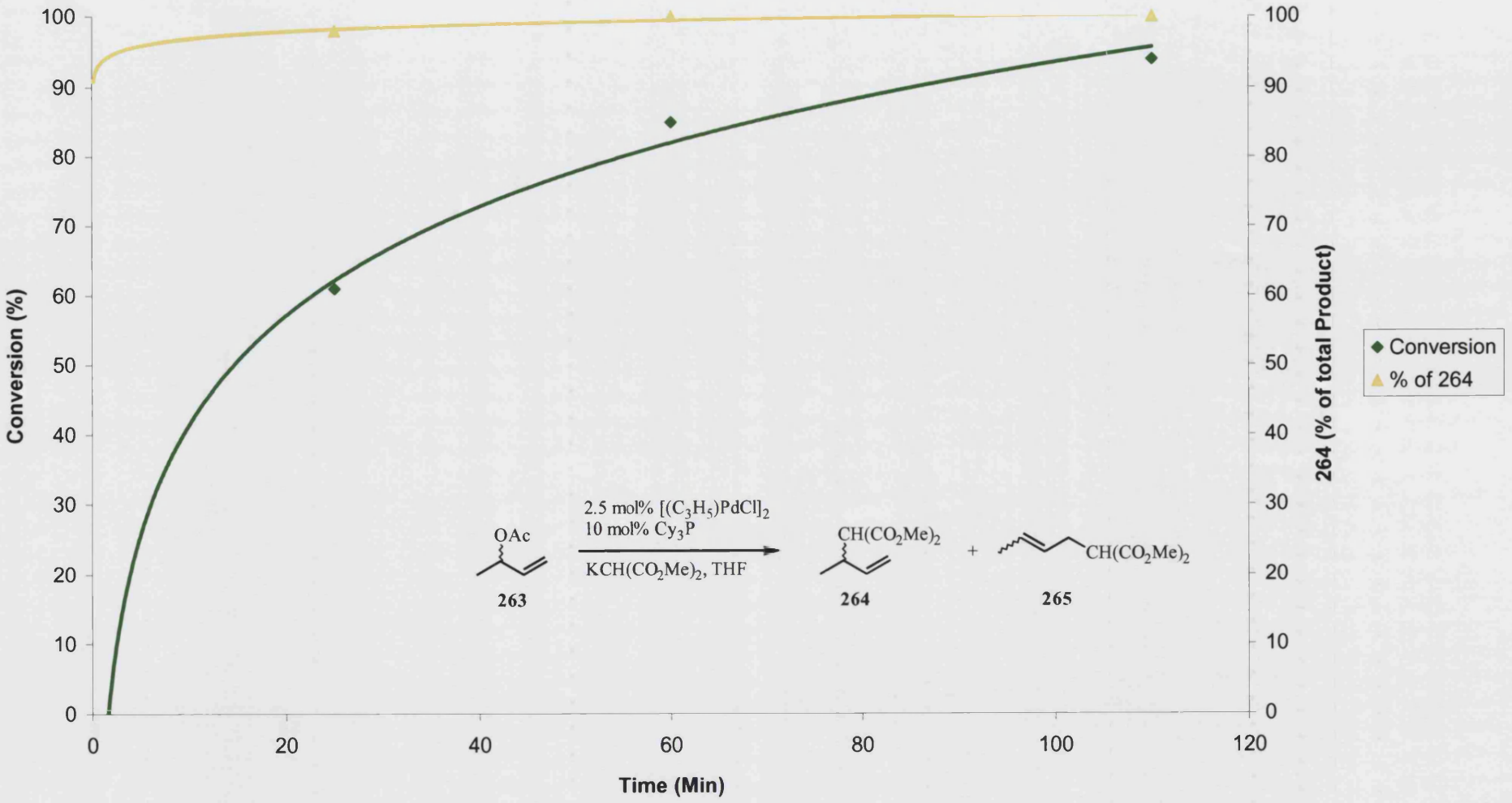
The reaction of acetate **263** with $NaCH(CO_2Me)_2$ in DCM was followed by GC. **Graph 4** shows the % conversion against time for this reaction as well as the change in the ratio of branched to linear products against time.

Graph 5 shows the % conversion against time for the reaction of acetate **263** with $KCH(CO_2Me)_2$ in THF.

Graph 4-Reaction of branched acetate 263 with dimethylmalonate



Graph 5-Reaction of branched acetate 263 with dimethylmalonate



Use of Other Nucleophiles

With the intention of finding out more about the mechanism of this reaction and to explore its synthetic scope, we tested a number of other nucleophiles.

Di-*t*-butyl malonate (**Scheme 105**) afforded similar results to dimethyl malonate used in **Scheme 101**. The results of this study are outlined in **Table 10**.

Scheme 105

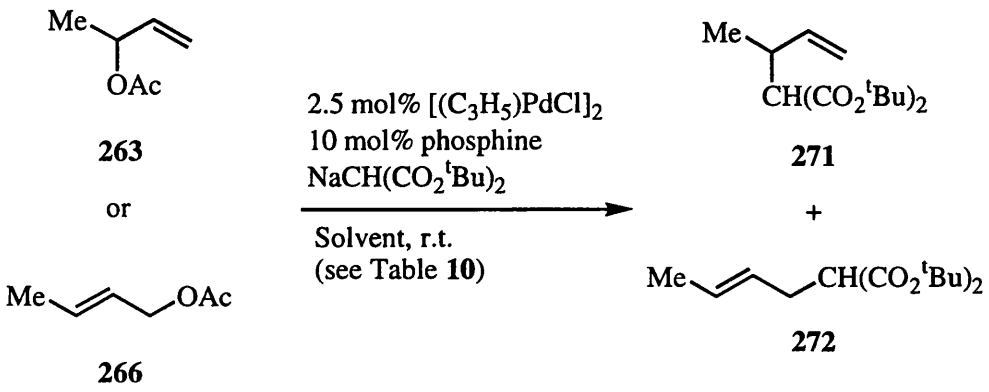


Table 10. Regiocontrol in the reaction of di-*t*-butylmalonate with substrates **263** and **266**.

Entry	Substrate	Ligand	Solvent	**271/ 272**[b]	time[c] (h.)
1	**263**	Ph_3P	THF	1.4:1	1
2	**263**	Cy_3P	THF	58:1[d]	1
3	**263**	Ph_3P	DCM	1:1[e]	16
4	**263**	Cy_3P	DCM	40:1	
5	**266**	Ph_3P	THF	1:1.1	1
6	**266**	Cy_3P	THF	1:1.6	1
7	**266**	Cy_3P	DCM	1:1.3	30[f]

[a] All reactions run using 2.5 mol% of $[(C_3H_5)PdCl]_2$ catalyst and 10 mol% ligand, 1.5 eqiuv. of $NaCH(CO_2Me)_2$ nucleophile at r.t.
[b] Ratio of **271/272** determined by GC and confirmed .
[c] All the reactions proceeded to 100% conversion except in the cases noted. Small amounts of disubstitution were observed.
[d] 81% isolated yield of **271** and **272**. 5% disubstituted product was isolated.
[e] Interconversion between the branched acetate **263** and linear acetate **266** was observed during the reaction by GC.
[f] 86% conversion after 30 h.

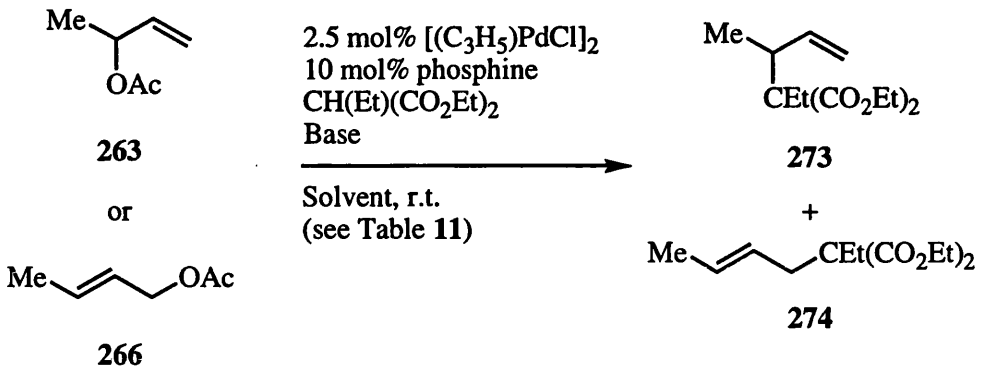
The products **271** and **272** were characterised using ^1H and ^{13}C NMR.

For the branched product **271** an AMX type coupling was observed, which is typical of terminal allyl protons. The terminal protons =C*H*$_2$ appeared at 4.99 ppm and 5.08 ppm, whereas C*H*= was observed at 5.80 ppm. The *trans* coupling constant J_{MX} was typical at 18.4 Hz. The *cis* coupling constant J_{AX} was found to be 10.5 Hz. and the *gem* coupling constant J_{AM} was 1.2 Hz. A one proton multiplet was observed at 2.82 ppm which was assigned to C*H*CH=CH$_2$. Two nine proton singlets were also observed at 1.44 and 1.46 ppm and were assigned to the *t*-butyl protons. The ^1H NMR pattern observed for this compound was very similar to that of the branched dimethyl malonate substituted compound **264**.

Once again high regioselectivities were obtained when the branched starting material **263** was subjected to the allylic substitution reaction. For example, whereas Ph_3P affords a product distribution of approximately 1:1 **271**:**272** with this nucleophile, selectivities of 58:1 in favour of the branched product were obtained when Cy_3P was used as the ligand (entry 2). All the reactions were followed by GC. It was interesting to discover that in the reaction of Ph_3P in DCM, although pure branched acetate was used as the starting material, interconversion between the branched and linear acetates was observed (entry 3). This may account for the fact that this reaction took longer to reach completion. On the other hand, unfortunately no regioselectivity was obtained with the linear acetate for the Cy_3P/Pd catalysed reaction (entries 6 and 7), as was also the case using dimethylmalonate nucleophile.

We were concerned that the linear products may be more susceptible to diallylation than the branched isomers, thereby distorting the true ratio of products. In order to completely eliminate the possibility of diallylation, we also employed the mono-substituted, diethyl ethyl malonate (**Scheme 106**). The results obtained with this bulky nucleophile show that good regioselectivity could now be obtained from both the branched acetate **263** and also that the linear acetate **266** now proceeded with good memory to provide the linear product **274** with good regioselectivity.

Scheme 106



The products **273** and **274** were characterised using ^{1}H and ^{13}C NMR.

For the branched product **273**, the same type of AMX pattern was observed for the terminal allyl protons, as was for the other branched compounds **264** and **271**. The methyl protons were observed as a doublet at 1.08 ppm. with a coupling constant of 6.6 Hz. The sp^3 proton that appeared at 2.84 ppm. shared the same coupling constant at 6.6 Hz. and was assigned to be Me*CH*CH=.

On the other hand, the linear product **274** was observed to have the Me doublet at a downfield shift of 1.63 ppm. in comparison to the branched product **273**. The ^{1}H NMR spectrum also displayed a two proton doublet at 2.56 ppm. assigned to CH=CHCH_2. There were two protons in the alkene region at 5.24 ppm and 5.51 ppm. which were attributed to =CH and CH= respectively.

The results of the preliminary study carried out with this nucleophile are shown in **Table 11.**

Table 11. Regiocontrol in the reaction of $NaC(Et)(CO_2Et)_2$ with substrates **263** and **266.**

Entry	Substrate	Ligand	Solvent	**273/ 274**[b]	time[c] (h.)
1	**263**	Ph_3P	THF	1:3	1
2	**263**	Cy_3P	THF	14:1[d]	1
3	**263**	Ph_3P	DCM	1:3	50% conversion[e]
4	**263**	Cy_3P	DCM	14:1	1
5	**266**	Cy_3P	THF	1:11	~ 6
6	**266**	Cy_3P	DCM	1:7.4[f]	~ 9

[a] All reactions run using 2.5 mol% of $[(C_3H_5)PdCl]_2$ catalyst and 10 mol% ligand, 1.5 eqiuv. of $NaCH(CO_2Me)_2$ nucleophile at r.t.
[b] Determined by GC and checked by ^1H NMR.
[c] All the reactions proceeded to 100% conversion except in the cases noted.
[d] 97% isolated yield
[e] only 50% conversion by GC after 17 h. Interconversion between the branched acetate **263** and linear acetate **266** was observed during the reaction by GC.
[f] 88% isolated yield

These results show that once again Cy_3P exhibits a very different product distribution to that of Ph_3P. Starting with the branched substrate **263**, Ph_3P affords **273**:**274** (branched/linear) products in the ratio of 1:3 with a preference for the linear product (entry 1). In comparison, for the corresponding reaction, Cy_3P exhibits a good memory effect even for this bulky nucleophile and a reversal of the product distribution is observed. Hence, starting with the branched acetate **263** Cy_3P affords a product ratio of 14:1 in favour of the branched isomer, thereby preserving the regichemistry of the starting material (entry 2). This is only slightly lower than the regioselectivity obtained when $NaCH(CO_2Me)_2$ was used as nucleophile. The larger size of $NaCEt(CO_2Et)_2$ might account for this result. Nevertheless the results obtained in this reaction help us to see the true

dimensions of the regioselectivity since disubstitution is not possible with this nucleophile.

Whereas the regioselectivity observed with the $NaCH(CO_2Me)_2$ nucleophile in DCM was considerably higher than the reaction carried out in THF (see **Table 7**); it was observed that the reaction gave the same result in DCM as it did in THF when $NaCEt(CO_2Et)_2$ was employed as the nucleophile (entries 2 and 4). It is difficult to account for this result.

One might argue that disubstitution might have some effect on this difference. (The linear product **265** could be more reactive towards disubstitution, as a result of steric reasons, compared with its regioisomer **264**, thereby distorting the true ratio of branched to linear products **264**:**265**). However, as outlined in **Table 7**, more disubstitution product was isolated for the THF reaction compared to that of DCM reaction. So it would be reasonable to conclude that disubstitution is not responsible for the enhanced regioselctivity for the $NaCH(CO_2Me)_2$ and DCM combination. In fact it appears that this combination might have unique properties. One of the reasons for this argument is that as discussed earlier, the reaction of the linear acetate does not proceed in DCM when $NaCH(CO_2Me)_2$ was used as the nucleophile. However, as **Table 11** shows this is not the case when diethyl ethylmalonate is used as the nucleophile. In fact, $NaCEt(CO_2Et)_2$ reacts with linear acetate **266** in DCM to afford **273**:**274** products in 88% yield and in 1 : 7.4 regioselectivity in favour of the linear product (entry 6). Likewise the reaction of the linear substrate in THF affords products with a slightly higher selectivity in favour of the linear product (entry 5). Pleasingly, the reaction outlined in **Scheme 106** displays high levels of regioselectivity, as might be expected from a memory

effect. Consequently, starting from the branched acetate afford the branched product and starting from the linear acetate yield the linear product.

Once again in the reaction of Ph_3P interconversion between the two starting materials was observed when DCM was employed as the solvent (entry 3).

The results presented on **Table 11** show that the branched acetate reacted faster than its linear isomer. This result seems to be in agreement with the results of the $NaCH(CO_2Me)_2$ reaction (**Graph 3**), whereby there was a rate difference between the reactions of the branched and linear acetates, **263** and **266**. However, since these reactions (**Table 11**) were not carried out in the same reaction flask, we thought that a competition experiment would be useful in confirming these results. We also envisaged that data obtained on rates of reactions could be useful in obtaining information about the mechanism and this could allow us to design reactions which would lead to higher regio- and enantioselectivities.

We showed on **Graph 3** that in DCM, branched acetate reacts faster than the linear isomer. We were interested to find out whether this phenomenon was also applicable to other nucleophiles.

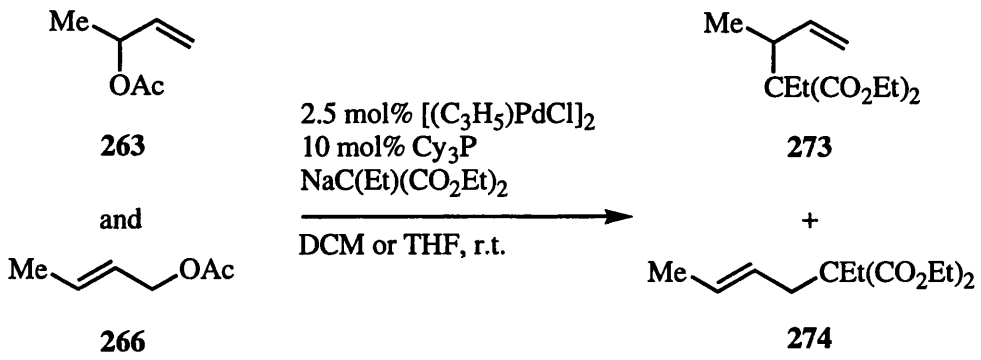
A 1:1 mixture of branched and linear acetates **263** and **266** in DCM was subjected to the palladium catalysed allylic substitution reaction with diethylethyl malonate as the nucleophile (**Scheme 107**) and the reaction was followed by GC. It was observed that after 1 h. all of the branched acetate **263** had reacted and the branched to linear product ratio (**273**:**274**) was 8.5:1 in favour of the branched product, confirming that more of the branched acetate **263** had reacted. In comparison, it took approximately 24 h. for all of the linear acetate to be consumed. The regioselectivity obtained at the end of the competition experiment was in agreement with the individual reactions themselves. The ratio of the

branched to linear products (**273**:**274**) at the end of the reaction was 2.5:1. This result would account for the branched acetate **263** forming products in a ratio of 14:1 (**273**:**274**) and the linear acetate **266** forming products in a ratio of 7:1 (**273**:**274**).

For comparison, a 1:1 mixture of branched and linear acetates **263** and **266** were also was subjected to the same reaction in THF (**Scheme 107**). It was found that, once again, branched acetate is consumed within the first hour and indeed it takes longer for the linear acetate to react. The regioselectivity at the end of this reaction was 1.3:1 **273**:**274** (branched/ linear products). This is in agreement with branched acetate forming products **273**:**274** in a 14:1 ratio and linear acetate forming products **273**:**274** in a 1:11 ratio.

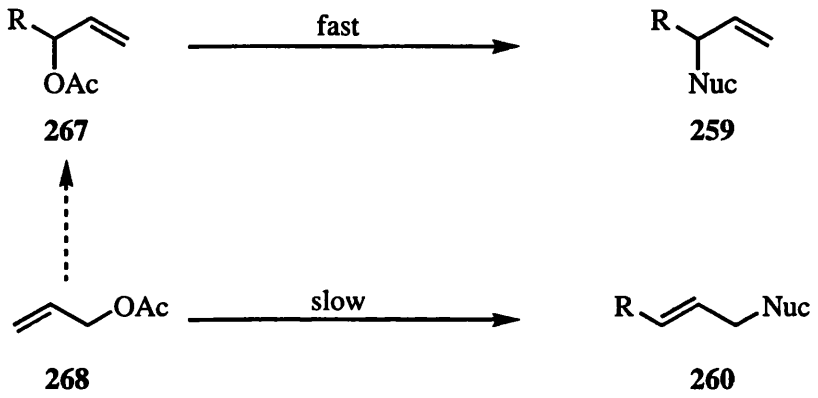
Nevertheless, the linear acetate does get completely consumed in both DCM and THF when diethylethyl malonate is employed as the nucleophile. An additional observation is that the linear acetate reacts faster in THF than it does in DCM.

Scheme 107



It is quite interesting to see that the branched acetate reacts faster than the linear acetate under exactly the same conditions. This implies that if we could find a way of converting linear starting material into branched starting material, we could form branched product from linear starting material, hence achieving 'kinetic discrimination'(**Scheme 108**). The proviso that the rate of this reaction must be faster than the reaction which forms branched product.

Scheme 108 Possibility of forming branched products from branched starting material?



Effect of Leaving Groups on Regioselectivity

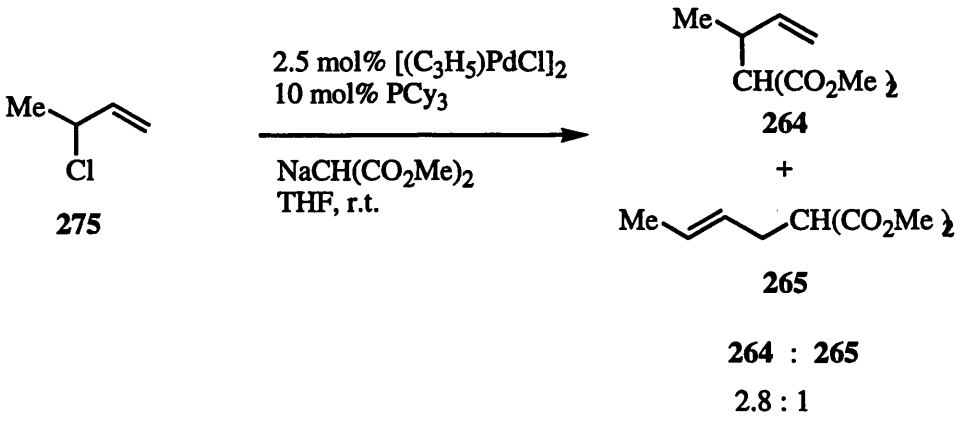
If our proposal is correct and that the leaving group co-ordinates to the palladium in the intermediate π-allyl palladium complex along with one of the phosphines, this would imply that the leaving group could have an important impact on the reaction and the regioselectivity. In the same way that the ligand can impose different steric and electronic properties, the leaving group can also function as a ligand and hence affect the properties of the metal centre in the intermediate complex. In this respect, several factors are of importance in determining the regiochemical outcome. The electronic properties of the leaving group, the

binding strength to the metal centre, the ease of ligand exchange and co-ordination ability are all of relevance.

The model substrates chosen for examination was allyl chloride **275,** whereby the leaving group is chloride rather than acetate (**Scheme 109**). A literature search for this reaction uncovered only one publication[237] whereby 89% of product is obtained using $Fe(CO)_2(NO)_2$ as the catalyst.

In order to ensure that the reaction did not proceed in the absence of catalyst, we also ran a 'standard background reaction' in the absence of catalyst. After 24 h no product was observed. In comparison, the reaction with the palladium catalyst showed the presence of product, by TLC, after 1.5h. However one of the problems we had with this substrate was that its volatility hindered monitoring of the reaction progress and unfortunately the peak corresponding to this compound co-eluded with that of the solvent (THF) on GC. We therefore decided to stir the reaction for 24 h before analysis.

Scheme 109

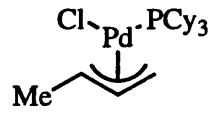


After 24h 40% of product was isolated as a mixture of branched and linear isomers, in addition to 7% of disubstitution product. GC showed a branched:

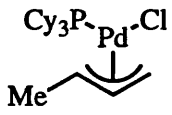
linear (**264**:**265**) ratio of 2.8:1. ^{1}H NMR analysis indicated the branched: linear ratio to be 2.4:1 **264**:**265**.

In comparison with the results we had obtained with acetate **263** and dimethylmalonate so far, the regioselectivity of this reaction seemed very poor. This result demonstrates that the leaving group is important in determining the regioisomeric product distribution. This outcome is also good evidence to support our theory that only one phosphine ligand is actually involved in the intermediate η^3-allyl palladium complex. According to our postulated mechanism the intermediate palladium complexes would be **276a** and **276b**.

Scheme 110



276a



276b

Why should these complexes proceed with less selectivity than the corresponding acetate compounds?

It is worth mentioning here a study performed by Hayashi[238] who reports that the reaction in **Scheme 111** could be fabricated to be purely regioselective in favour of the linear product **279** realised by the addition of a catalytic amount of LiI. The reaction was not strongly affected by the addition of lithium fluoride, chloride or bromide with branched isomer being formed with about 20% regioselectivity.

Scheme 111

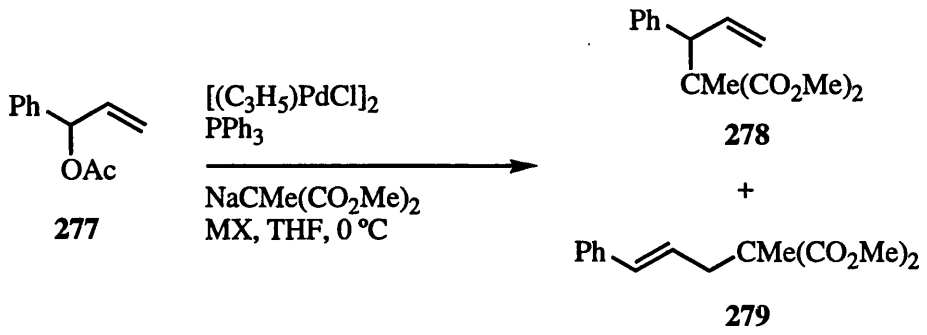


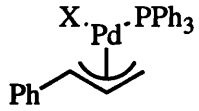
Table 12. Effect of lithium salts on allylic alkylation of acetate **277**. [238]

MX	**278/279**
none	23:77
LiI	0:100
LiF	22:78
LiCl	18:82
LiBr	20:80
NaI	2:98

All reactions were carried out in THF: THF (1.0 mL), allylic acetate (0.20 mmol), $NaCMe(CO_2Me)_2$ (0.40 mmol), $[(C_3H_5)PdCl]_2$ (0.002 mmol) and Ph_3P ligand at 0 °C. The ratio of Pd:Phosphine = 1 : 2. 0.1 equiv. of MX was used.

A comparison of the ^{13}C NMR spectra of **280** and **281** (**Scheme 112**) showed that the chemical shift for the C-3 of π-allyl group of **281** appears at lower field than that for **280** by 6.5 ppm and the chemical shift for C-1 of **281** appears at higher field than that for **280** by 3.1 ppm.

Scheme 112



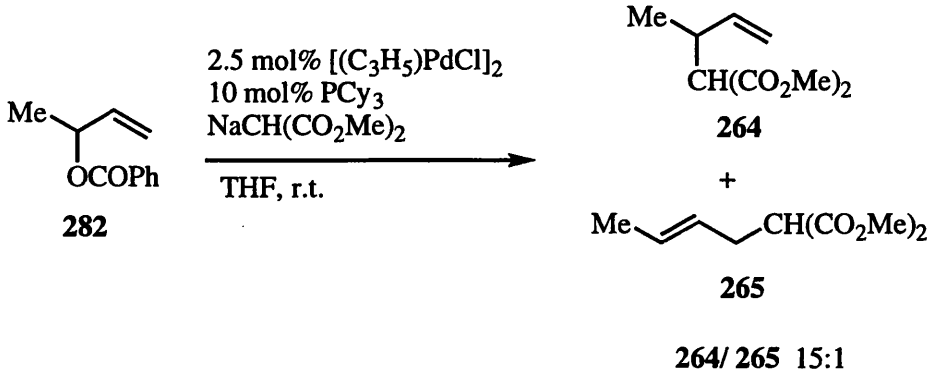
280 X= Cl
281 X= I

Hayashi postulated that the difference in chemical shifts may support the idea that C-3 carbon of the iodide complex **281** undergoes the nucleophilic attack giving linear isomer **271** more selectively than that of **280**.

The results obtained by Hayashi show how the identity of the groups attached to the palladium centre can have a major role in determining the site of nucleophilic attack.

Another substrate examined was allyl benzoate **282**, featuring a benzoate leaving group rather than an acetate (**Scheme 113**). The reaction of this substrate with dimethyl malonate results in the formation of products **264**:**265** in a 15:1 ratio, as determined by GC.

Scheme 113



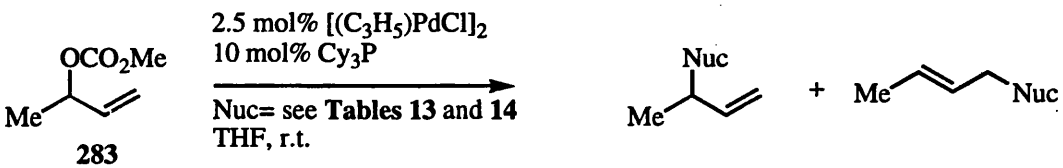
264/ 265 15:1

This result shows that, in terms of the regioselectivity of this reaction, there is not much difference between using an acetate or a benzoate leaving group i.e. substrates **263** and **282** respectively.

Allyl carbonates are one of the most commonly used substrates in palladium chemistry. They are known to be more reactive than the corresponding acetates. Their reactions proceed with the loss of CO_2 to generate the relevant alkoxide. We therefore contemplated to test the reaction of these substrates with the Pd / Cy_3P catalyst.

Carbonate **283** was prepared according to literature procedure[239] with the reaction of 1-buten-3-ol along with methylchloroformate in pyridine.

Scheme 114



283

Nuc= $CH_2(CO_2Me)_2$	**264**	**265**
Nuc= $CEt(CO_2Et)_2$	**273**	**274**

Table 13 shows the results obtained from the reaction of carbonate **283** with dimethylmalonate and diethylethylmalonate in THF when NaH was used as the base (**Scheme 114**). We included results obtained from the reaction of acetate, **263**, in this Table in order to allow us to make comparisons between acetate and carbonate as leaving groups.

Table 13 – Comparison of acetate and carbonate leaving groups, using NaH as the base.

Entry	Substrate	Nucleophile	Time (min.)	**branched/ linear** products[b], [c]
1	**263**	$NaCH(CO_2Me)_2$	1h	16: 1
2	**283**	$NaCH(CO_2Me)_2$	10[d]	26: 1
			40	43: 1
3	**263**	$NaCEt(CO_2Et)_2$	1h	14: 1
4	**283**	$NaCEt(CO_2Et)_2$	10[d]	15: 1

[a] All reactions run using 2.5 mol% of $[(C_3H_5)PdCl]_2$ catalyst and 10 mol% Cy_3P ligand, 1.5 eqiuv. of nucleophile, THF solvent at 20 °C. In all cases conversion was 100%, as determined by GC. Isolated yield between 80-85%.
[b] Products **264/265** when $NaCH(CO_2Me)_2$ was used and **272/274** when $NaCH(CO_2Me)_2$ was used as the nucleophile.
[c] Determined by GC and confirmed by ^1H NMR.
[d] Reaction was complete in 10 min.
[e] 80% isolated yield, 7% disubstitution product isolated.

One conclusion we can draw from this table is that, comparing entry 1 to entry 2 and comparing entry 3 to entry 4, it seems that the regioselectivities obtained from substrate **283**, which has a carbonate leaving group, are slightly higher than that of acetate **263**, when both dimethyl malonate and diethylethylmalonate are used as nucleophiles.

Moreover we found that in most cases the reactions take only between 10 to 20 min to reach completion, while it takes longer for the corresponding acetate.

We also carried out a range of experiments using KH as the base, rather than NaH, with both acetate and carbonate as the substrates using both dimethylmalonate and diethylethyl malonate nucleophiles. The results are summarised in **Table 14**.

A comparison between the **Tables 13** and **14** show that the regioselectivities obtained when KH is used as the base seem to be higher than the corresponding reactions carried out in the presence of NaH e.g. compare entry 1 (**Table 13**) and entry 1 (**Table 14**).

Table 14 –Comparison of acetate and carbonate leaving groups, using KH as base.

Entry	Substrate	Nucleophile	time	**branched/linear** products[b], [c]
1	**263** (Acetate)	$KCH(CO_2Me)_2$	2 h	23:1[f]
2	**283** (Carbonate)	$KCH(CO_2Me)_2$	10 min	27:1
			30 min	46:1
3[g]	**263** (Acetate)	$KCEt(CO_2Et)_2$	30 min	branched only
			1 h	191:1
			2.5 h	93:1
			3.5 h	54:1
			4.5 h[e]	47:1
			48 h	27:1
			60 h	32:1
4	**283** (Carbonate)	$KCEt(CO_2Et)_2$	10 min[d]	30:1
			40 min	50:1
			120 min	80:1

[a] All reactions run using 2.5 mol% of $[(C_3H_5)PdCl]_2$ catalyst and 10 mol% Cy_3P ligand, 1.5 eqiuv. of nucleophile, THF solvent at 20 °C. In all cases conversion was 100%, as determined by GC.
[b] Products **264/265** when $NaCH(CO_2Me)_2$ was used and **272/274** when $NaCH(CO_2Me)_2$ was used as the nucleophile.
[c] Determined by GC and confirmed by ^1H NMR.
[d] Reaction was complete in 10min.
[e] This reaction took 4.5h. to reach completion.
[f] 80% isolated yield of **264** and **265**. >1% disubstitution product isolated.
[g] 95% isolated yield of **272** and **274**.

As revealed in **Table 13** and **Table 14**, whilst following some of these reactions by GC, we found that the ratios of branched/linear products can change as the reaction proceeds.

For example, this is observed in the case of potassium diethylethylmalonate (entries 3 and 4 in **Table 14**). This fluctuation is observed even though disubstitution is not possible for this nucleophile i.e. disubstitution can not be responsible for this result. In the case of entry 3, more of the branched product is formed at the beginning of the reaction and the ratio of branched to linear drops as the reaction proceeds. However, although the reaction reaches completion after 4.5 h the ratio continues to drop even after the starting material is consumed.

On the other hand entry 4 shows that when carbonate **283** is the starting material the reaction reaches completion after 10 min. after which time the ratio of **273**:**274** (branched / linear) increases, even though there is no more starting material left.

One of the possible reasons that could lead to deviation of the results and cause fluctuations is that the more samples taken out of a reaction, for analysis, the more one would be disrupting the homogenous nature of the system hence introducing the possibility of increased error.

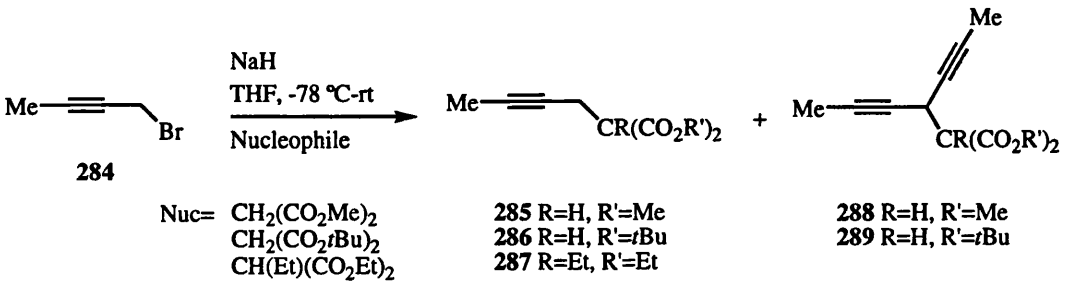
Nevertheless, the regioselectivities presented in **Tables 13** and **14** are very high and pleasing. However, this meant that on the GC traces, the peaks corresponding to the *cis*- and *trans*- linear products were very small compared to the branched isomer, which sometimes made their identification very hard, especially when there were other very small impurity peaks around the same region. In addition, the smaller the peaks are, the more chance there is for GC error.

Identification of *Cis*- Linear Isomers

The fact that only very small amounts of *cis*- and *trans*- linear isomers were being formed through allylic alkylation using Pd/Cy_3P meant that it was sometimes difficult to identify the peaks corresponding to those of the linear compounds on GC. As *cis*- was the minor regioisomer it was particularly difficult to isolate and identify.

We therefore decided to form these compounds *via* a different route. We planned to form the *cis*-isomers through hydrogenation of the alkylated butyne compounds **285-287** with Lindlar catalyst. This should prevent the formation of any of the *trans*-linear or branched isomers.

Scheme 115



Compounds **285**, **286** and **287** were formed *via* the substitution reaction of malonates with 1-bromo-2-butyne (**Scheme 115**).

The reaction of 1-bromo-2-butyne with dimethylmalonate formed **285**, in 36% isolated yield, as a colourless oil. Disubstituted product, **288** was also formed as a colourless solid, in 14% yield (i.e. from 28% starting material). The compounds were identified *via* ^1H and ^{13}C NMR analysis.

The reaction of di-*tert*-butylmalonate with 1-bromo-2-butyne led to the formation of butyne **286** and disubstituted product **289** in 40% and 8% yield respectively.

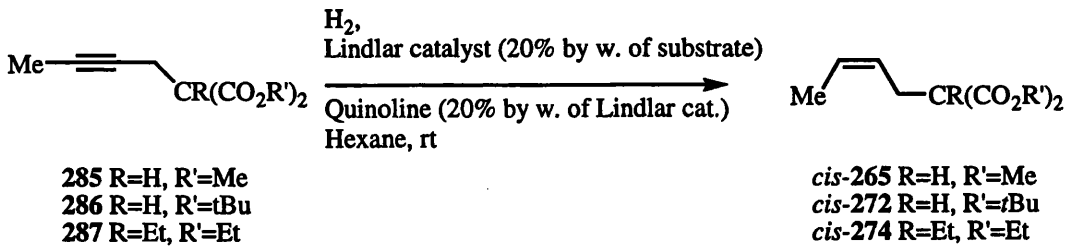
Since these reactions were carried out for the purposes of synthesising authentic samples for identification, the yields have not been optimised. The compounds were identified *via* analysis of ^{1}H and ^{13}C NMR.

^{1}H NMR spectrum of butyne **286** displayed the methyl singlet at 1.75 ppm. A one proton triplet at 3.30 ppm was assigned to $CH(CO_2{}^{t}Bu)_2$. The *tert*-butyl protons were identified as a singlet integrating to 18 protons which was observed at 1.47 ppm.

In the same way, the reaction of diethylethyl malonate with 1-bromo-2-butyne afforded **287** in 98% yield as a colourless oil. The product was identified *via* ^{1}H and ^{13}C NMR analysis. The ^{1}H NMR spectrum displayed a three proton signal assigned to the methyl protons at 1.72 ppm. The ethyl ester protons were identified at 1.23 ppm ($CO_2CH_2CH_3$) and 2.05 ppm ($CO_2CH_2CH_3$). The information obtained from IR and accurate mass spectra supported this structure.

Hydrogenation of compounds **285, 286** and **287** using Lindlar catalyst led to the formation of the *cis*- isomers **265, 272,** and **274 (Scheme 116)**.

Scheme 116



285 R=H, R'=Me
286 R=H, R'=tBu
287 R=Et, R'=Et

cis-**265** R=H, R'=Me
cis-**272** R=H, R'=*t*Bu
cis-**274** R=Et, R'=Et

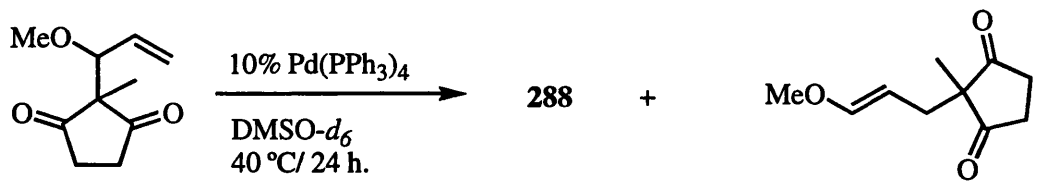
The hydrogenation products were formed in quantitative yield in 1h. The products were characterised using ^1H NMR analysis. The GC analysis of these authentic compounds reconfirmed the position of the retention times.

Does Cy_3P/ Pd Cleave C-C Bonds?

Although not common, there are a number of reports which have shown that carbanionic species can play alternatively the role of either a nucleophile or a leaving group in palladium catalysed allylic substitution, thereby allowing the reversibility of the attack on the π-allyl complex.

For example, Cazes[240] has shown that treatment of compound **288** with 0.1 equivalent of tetrakis(triphenylphosphine)palladium in DMSO-d_6 at 40°C for 24h. leads to mixtures of two isomers **288** and **289** in the ratio 30:70, demonstrating that 2-methyl-1,3-cyclopentanedione can act both as a nucleophile and a leaving group (**Scheme 117**).

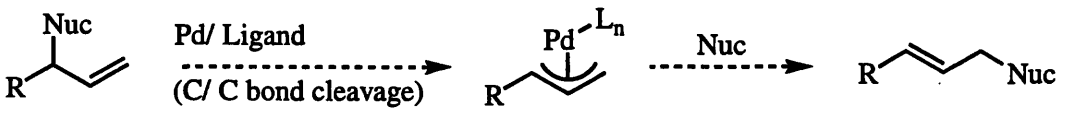
Scheme 117



288 30:70 **289**

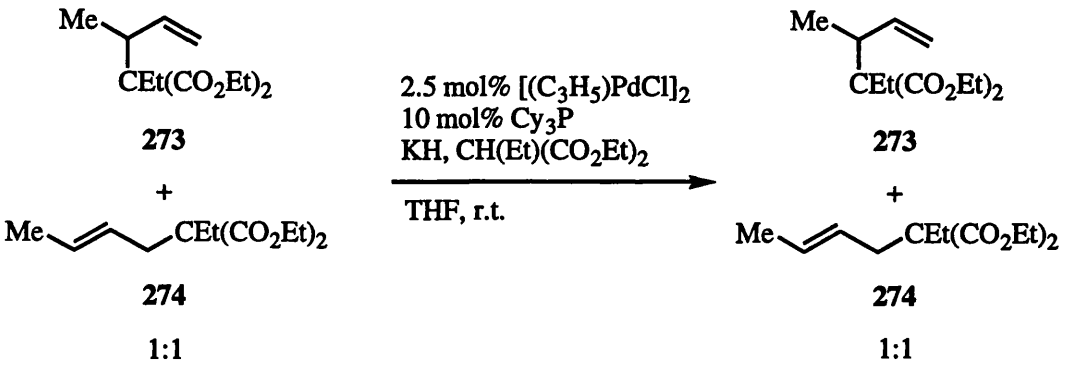
We were therefore curious to find out whether the Cy_3P/Pd catalyst would catalyse the isomerisation of alkylated allylic compounds, *via* the cleavage of carbon-carbon bonds (**Scheme 118**).

Scheme 118



To test this theory, we carried out a reaction on a one to one mixture of **273** and **274** in the presence of palladium catalyst and nucleophile in THF (**Scheme 119**).

Scheme 119



Any changes in the ratio of **273**:**274** would imply cleavage of the carbon/ nucleophile bond. The reaction was followed by GC for 20h. However, we did not observe any change in the ratio of **273**:**274** under these particular experimental conditions.

Hence, we conclude that the fluctuations of branched/ linear products in entries 3 and 4 (**Table 14**) could not have been due to reisomerisation.

Use of Malonitrile as the Nucleophile

We also examined the use of malonitrile as a nucleophile in the tricyclohexylphosphine-palladium catalysed allylic substitution reaction of acetate **263** (**Scheme 120**). A literature search showed no literature precedence on

compounds **291** and **292**. There seems to be no precedence for the use of malonitrile in the palladium catalysed allylic substitution reactions.

Compounds **291** and **292** were identified by ^{1}H and ^{13}C NMR analysis.

Once again the general pattern observed for the ^{1}H NMR spectrum of the branched product **291** is very similar to that of the other branched products synthesised in this series. The ^{1}H NMR spectrum displayed a methyl doublet at 1.36 ppm and a one proton multiplet was observed at 2.78-2.93 ppm which suggested the presence of C*H*CH=CH_2. There was also a one proton doublet at 3.69 ppm assigned to C*H*$(CN)_2$. In addition, the same pattern of AMX coupling was observed analogous to the other branched products synthesised. The information from accurate mass and IR spectroscopy also supported this structure.

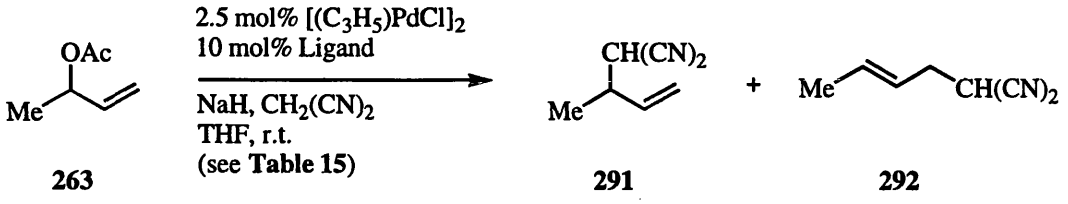
When acetate **263** was alkylated with 1.5 equivalents of sodium malonitrile using triphenylphosphine as the ligand a mixture of the products **291** and **292** were observed in the ratio of 2:1 (**Table 15**).

Switching the ligand to tricyclohexylphosphine revealed the same trend as the other nucleophiles we tested with this ligand. We were pleased to discover that this reaction gave almost exclusive formation of the branched product **291** (17:1).

Unfortunately the yield in both the Cy_3P and Ph_3P catalysed reactions was very low. Substantial amounts of the diallylation products (**Scheme 121**) were also isolated from both of the reactions. The disubstitution products were formed from the beginning of the reaction and their formation is largely responsible for the low yield in these reactions. In both the case of the Cy_3P and Ph_3P catalysed reactions 22% of the disubstitution products were isolated (i.e. from 44% starting material).

However, although GC analysis showed this to be a mixture of products as expected. These products were not separable by column chromatography.

Scheme 120



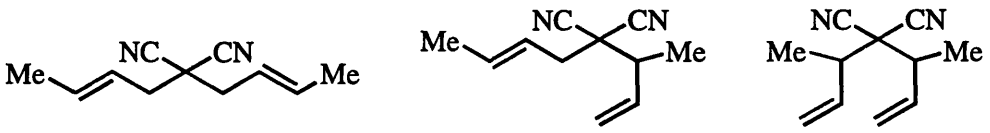
263 **291** **292**

Table 15. Use of malonitrile as the nucleophile in the palladium catalysed allylic substitution reaction

Substrate	Ligand	**291**:**292**[b]	Yield of **291** and **292** (%)	Yield of disubstitution product (%)
263	Ph_3P	2:1	27	22 (44)[c]
263	Cy_3P	17:1	28	22 (44)[c]

[a] Reactions run using 2.5 mol% of $[(C_3H_5)PdCl]_2$ catalyst and 10 mol% ligand, 1.5 eqiuv. of $NaCH(CN)_2$, THF solvent at 20 °C. In all cases conversion was 100%, as determined by GC.
[b] Determined by GC and confirmed by ^1H NMR.
[c] Based upon starting material.

Scheme 121

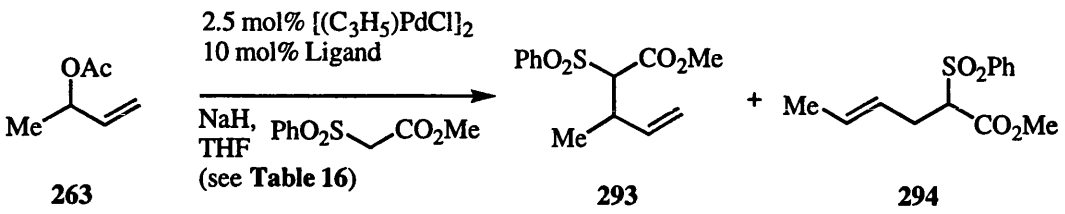


The use of Methylphenylsulfonyl acetate as the Nucleophile

The potential of methylphenylsulfonyl acetate as a nucleophile in the Pd/Cy_3P catalysed allylic substitution reaction was also tested (**Scheme 122**). Methyl phenyl sulfonyl acetate is a bulky nucleophile. Although its Ph_3P catalysed

reaction proceeds at room temperature to produce **293** and **294** in 73% yield, the Cy_3P catalysed reaction required heating in order to produce the substitution products in 66% yield.

Scheme 122



263 **293** **294**

Compounds **293** and **294** were identified by ^1H and ^{13}C NMR analysis.

The branched product **293** was observed as a mixture of two diastereomers. Two methyl doublets were observed at 1.11 and 1.36 ppm. Two CO_2Me singlets were also observed at 3.47 and 3.62 ppm. In addition, two doublets were observed for C*H*(SO_2Ph), one for each diastereomer, at 3.92 and 3.97 ppm. Aromatic protons were visible between 7.64 and 7.93 ppm attributed to SO_2Ph. The same general pattern for terminal alkene group was also observed showing that this was the branched product.

In comparison, the methyl signal for the linear isomer **294** was once again at a downfield shift of 1.61 ppm. A two proton multiplet at 2.56-2.74 ppm as well as the presence of two alkene protons, one at 5.20-5.30 ppm and another at 5.49-5.58 ppm identified this as the linear isomer.

Although the reactions of all the other nucleophiles we tested with Pd/Cy_3P catalyst were highly regioselective, as discussed earlier, and proceeded with a 'memory effect' to afford the desired branched regioisomers selectively; we found

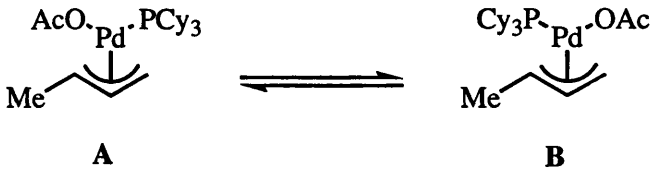
that a mixture of regioisomeric products were formed when methyl phenyl sulfonyl acetate was employed as the nucleophile in this reaction (**Table 16**). This might be partly due to the fact that this is a bulky nucleophile. Whereas the Pd/ Ph_3P catalysed reaction proceeds at room temperature in 1 h, the corresponding reaction catalysed by Pd/Cy_3P takes a longer time to reach completion. This might therefore allow more time for the intermediate Pd complexes **A** and **B** (**Scheme 123**) to equilibrate thereby scrambling the regioselectivity of the reaction. Hence, a 'memory effect' did not seem to be associated with this nucleophile.

Table 16. Palladium catalysed allylic substitution of But-2-enyl Acetate **263** with Methyl phenyl sulfonyl acetate

Substrate	Ligand	**293**:**294**[b]	Yield of **293** and **294** (%)
263	Ph_3P[c]	1 : 2.1	73
263	Cy_3P[c]	1.4 : 1	30
263	Cy_3P[d]	1.6 : 1	66

[a] Reactions run using 2.5 mol% of $[(C_3H_5)PdCl]_2$ catalyst and 10 mol% ligand, 1.5 eqiuv. of NaCH(SO2Ph)(CO_2Me) and THF solvent.
[b] Determined by ^{1}H NMR.
[c] Reaction run at r.t.
[d] Reaction heated at reflux.
[e] All reactions produced ~6% disubstitution product.

Scheme 123

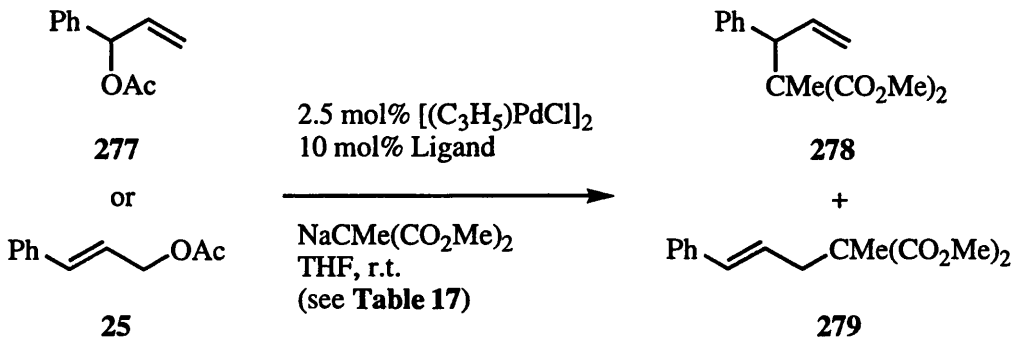


A **B**

Use of Cinnamyl Acetate and Isocinnamyl Acetate as the Substrates

In order to assess the synthetic scope of the 'memory effect' associated with Pd/Cy_3P catalysed reactions, we also tested the aryl-substituted cinnamyl acetate and the regioisomeric isocinnamyl acetate as substrates (**Scheme 124**). The results of these reactions are outlined on **Table 17**.

Scheme 124



Unfortunately the reaction of isocinnamyl acetate with dimethylmethyl malonate catalysed by Pd/Cy_3P did not seem to proceed with a 'memory effect'. Starting with the branched acetate **277** the ratio of the products **278:279** obtained was 15:85 in favour of the linear product. Therefore the regiochemical outcome of this reaction was very similar in this case to that of the Ph_3P catalysed reaction (23:77 in favour of the linear isomer).

It is difficult to explain this result. If the reaction mechanism proposed for the Cy_3P catalysed reaction in **Scheme 103** is indeed correct, one would expect to have obtained the branched product from the branched starting material for this reaction, as was the case with other substrates we studied. As demonstrated in **Scheme 125**, assuming that the reaction proceeds through η^3-allylpalladium complexes **A** and/or **B**, one would expect the equilibrium between these two complexes to lie towards complex **A**, in view of steric reasons. Nucleophilic

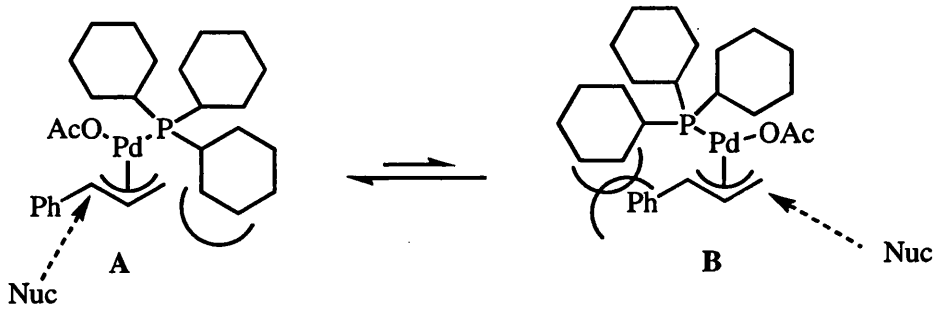
attack on complex **A** would result in the branched product. Therefore, we would have expected to obtain the branched product from the branched starting material. Hence, further mechanistic studies are required to explain this anomalous result.

Table 17. Palladium catalysed allylic substitution of isocinnamyl acetate **277** and cinnamyl acetate **25** with dimethylmethyl malonate.

Substrate	Ligand	**278** : **279**[b]	Yield (%) (**278** and **279**)
277	Ph_3P	23 : 77[c]	96
277	Cy_3P	15 : 85	96
25	Ph_3P	9 : 91[d]	99
25	Cy_3P	10 : 90	96

[a] Reactions run using 2.5 mol% of $[(C_3H_5)PdCl]_2$ catalyst and 10 mol% ligand, 1.5 eqiuv. of $NaCMe(CO_2Me)_2$ and THF solvent at r.t..
[b] Determined by ^1H NMR.
[c] Taken from reference [238]
[d] Taken from reference [242]

Scheme 125



The reaction of the regioisomeric cinnamyl acetate **25** resulted in the formation of the products **278** and **279** in a 10 : 90 ratio again in favour of the linear product. Therefore for the aryl-substituted acetates **25** and **277**, the Pd/ Cy_3P catalysed reaction seems to favour the linear product **279** irrespective of whether the branched or the linear starting material is utilised.

Use of Other Trialkylphosphine Ligands to Control Regioselectivity

Although in **Table 5** we showed that a wide range of other phosphines, including bulky electron rich arylphosphines, did not exhibit the same memory effect as tricyclohexylphosphine, we discovered that other bulky aliphatic phosphines do have a strong preference for conversion of the branched acetate **263** into the branched substitution product **264**.

Even using THF as the solvent, the ligands shown in **Table 18** all provide somewhat higher regioselectivity than tricycylohexylphosphine itself and warrant further investigation.

Table 18. Use of other bulky aliphatic phosphines in allylic substitution reactions

Substrate	Ligand	Products **264**/ **265**[b]
263	Cy_3P	16:1
263	$(c\text{-}C_5H_9)_3P$	24:1
263	$(i\text{Pr})_3P$	26:1
263	$(t\text{Bu})_3P$	43:1

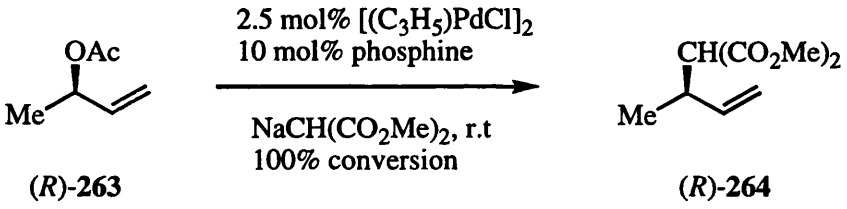
[a] All reactions run using 2.5 mol% of $[(C_3H_5)PdCl]_2$ catalyst and 10 mol% ligand, 1.5 eqiuv. of $NaCH(CO_2Me)_2$ nucleophile at r.t.
[b] Determined by GC.

Retention of Stereoselectivity Using Cy_3P

As we have demonstrated, when palladium catalyst is used along with Cy_3P, the reactions seem to proceed with retention of the regioisomeric identity of the starting material. In other words, the nucleophile seems to remember, and therefore attack, the allylic terminus that the leaving group has departed from. If the nucleophile could also remember which face of the allyl moiety the leaving group has left from, the reaction would lead to retention of stereochemistry.

Evans and Nelson have recently reported that enantiomerically pure branched acetate (S)-**263** undergoes substitution reaction with malonate with retention of stereochemistry and regiochemistry using a rhodium based catalyst.[229] However, it is expected that with palladium catalysts the enantiomeric excess of the substrate will be severely eroded by a π-σ-π process during the reaction, and indeed this is observed using a palladium catalyst in combination with Ph_3P. In the palladium catalysed allylic substitution of enantiomerically pure starting material, (*R*)-**263**, the product has been obtained with racemisation to afford **264** in 15% ee (**Scheme 126, Table 19**). In comparison when Cy_3P/ Pd is employed as the catalyst, the substitution product (*R*)-**264** is formed with significantly greater retention of stereochemistry.

Scheme 126



(*R*)-**263** (*R*)-**264**

Table 19. Partial retention of stereochemistry using Cy_3P

Ligand	Solvent	ee[b] (%)
Ph_3P	THF	15
Cy_3P	THF	64
Cy_3P	DCM	41

[a] All reactions run using 2.5 mol% of $[(C_3H_5)PdCl]_2$ catalyst and 10 mol% ligand, 1.5 eqiuv. of $NaCH(CO_2Me)_2$ nucleophile at r.t.
[b] Determined by ^1H NMR using the chiral shift reagent $Eu(hfc)_3$.

Conclusion

We have demonstrated that the use of tricyclohexylphosphine in palladium catalysed allylic substitution reactions leads to a 'memory effect'. Branched substrates afford branched substitution products preferentially and exhibit excellent regioselectivity. Linear acetates afford a mixture of branched and linear substitution products, although when a bulky nucleophile is used the selectivity for the linear substitution product increases.

We carried out the reactions on butenyl substrates (**256** and **257**, R=Me) with a range of different leaving groups and a range of different nucleophiles in order to get some insight into the mechanism and the synthetic scope of this reaction. One of the observations from these experiments was that the leaving group can have a major influence on the regiochemical outcome of the reaction. This suggests that the reactions might proceed *via* neutral complexes of the type [(allyl)Pd(OAc)(Cy_3P)] whereby the leaving group is co-ordinated to the palladium and therefore only one Cy_3P ligand is involved in the reaction. The fact that the reaction catalysed by Pd/Cy_3P, whereby only one equivalent of ligand per Pd was used, gave the same regioselectivity as that of the reaction catalysed by Pd/Cy_3P (1:2 equiv.) supports this argument.

Experiments using other bulky aliphatic phosphines such as tricyclopropylphosphine revealed that these ligands also have a tendency to form branched products from branched starting materials.

We have also discovered the Cy_3P ligand to be special in that it partially preserves the stereochemistry of the starting material, unlike other ligands such as Ph_3P when used along with Pd as the catalyst in palladium catalysed allylic substitution

reactions. We would normally expect the enantiomeric excess of a substrate to be eroded through a π-σ-π process.

Therefore more detailed mechanistic studies are required to uncover the origin of the 'memory effect' associated with Cy_3P. Development of a chiral version of this ligand that would catalyse reactions both with regioselectivity as well as stereoselectivity would also be of tremendous synthetic value to chemists.

In conclusion, allylic alkylation using Cy_3P as the ligand could provide insight into the mechanism of palladium-catalysed allylic substitution, which has recently been shown to be more complex than first thought of. Furthermore, the use of this cheap and commercially available ligand may be of great synthetic use by retaining the regiochemistry of allylic acetates in the alkylation products.

Chapter 4

Experimental

Experimental

General.

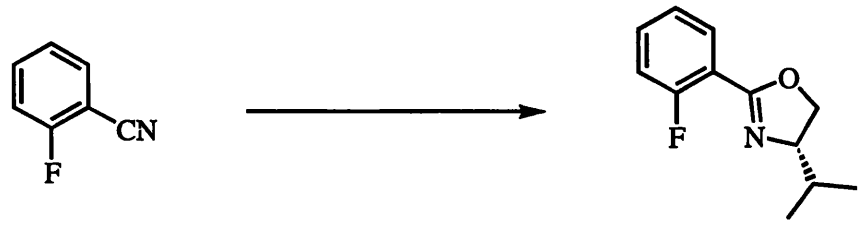
Commercially available solvents and reagents were used throughout without further purification, except for those described below which were purified as described. Solvents for reactions were HPLC grade, whereas during work-up and purification standard grade solvents were used. Where a solvent is described as dry, the standard grade solvent was distilled from an appropriate drying agent. THF was distilled from sodium benzophenone ketyl under nitrogen prior to use.

Analytical thin layer chromatography was carried out using plastic backed plates coated with Merck Kieselgel 60 GF_{254}. Plates were visualised using UV light (at 254 nm) and/or by staining with potassium permanganate or vanillin followed by heating. Flash chromatography was carried out using Merck Kieselgel 60 H silica. Pressure was applied via hand bellows. Samples were applied pre-absorbed on silica or as saturated solutions in an appropriate solvent.

Infra red spectra were recorded in the range 4000-600 cm^{-1} using a Perkin Elmer 1605 FT-IR spectrometer. Spectra were recorded as Nujol mulls or as neat samples. Elemental analysis was carried out on a Carbo-Erba Stametazione EA 1506 analyser. Melting points were measured on a Gallenkamp single stage apparatus and were uncorrected. ^{1}H and ^{13}C NMR spectra were recorded using Joel GX 270, Bruker GX 300 and Bruker GX 400 instruments at the frequency indicated and are referenced to TMS.

Experimental for Chapter 1

Synthesis of (4*S*)-2-(2-fluorophenyl)-4-isopropyl-1,3-oxazoline 211

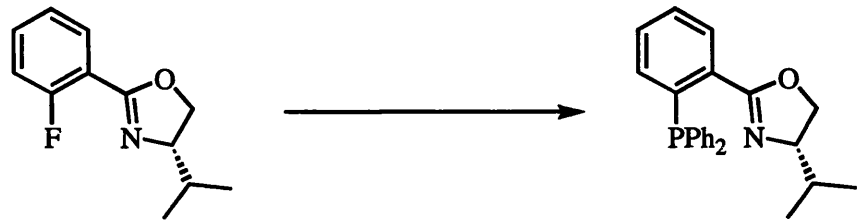


$C_{12}H_{14}FNO$
Exact Mass: 207.1059
Mol. Wt.: 207.2471
C, 69.55; H, 6.81; F, 9.17; N, 6.76; O, 7.72

Zinc chloride (0.27 g, 2 mmol, 0.05 equiv.) was dried in a three-necked round-bottomed flask by melting, drying under *vacuum* and cooling under nitrogen three times. After cooling to room temperature, 2-fluorobenzonitrile (4.3 mL, 4.8 g, 40 mmol, 1 equiv.) was added followed by (*S*)-valinol (5.79 mL, 5.36 g, 52 mmol, 1.3 equiv.). The mixture was heated at reflux under N_2 for 48 h. The crude mixture was dissolved in dichloromethane (100 mL) and then extracted three times with water (80 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (20% EtOAc/ light petroleum). The product was obtained as a yellow oil (2.88 g, 13.90 mmol, 35%); R_f 0.55 (20% EtOAc/ light petroleum); δ_H(270 MHz; $CDCl_3$) 0.92 (3H, d, *J* 6.8, CHC*H*$_3$), 1.02 (3H, d, *J* 6.8, CHC*H*$_3$), 1.87-1.94 (1H, m, C*H*$(CH_3)_2$), 4.07-4.20 (2H, m, CH_2O), 4.35-4.44 (1H, m, CHN), 7.09-7.91 (4H, m, Ar).

Identical to literature data.[85]

Synthesis of (4*S*)-2-(2-diphenylphosphinophenyl)-4-isopropyl-1,3-oxazoline 83



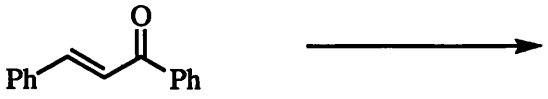
$C_{24}H_{24}NOP$
Exact Mass: 373.1595
Mol. Wt.: 373.4335
C, 77.19; H, 6.48; N, 3.75; O, 4.28; P, 8.29

To a flame-dried three-necked flask, was added potassium diphenylphosphide (22.4 mL, 11.20 mmol, 0.5M solution in THF, 1 equiv.) and this was heated at reflux. Following this, (4*S*)-2-(2-fluorophenyl)-4-isopropyl-1,3-oxazoline (2.31 g, 11.20 mmol, 1 equiv.) was added. The mixture was then stirred under reflux for 2 h, whereupon the red solution of the phosphide fades to a pale yellow. The reaction was then diluted with DCM (100 mL) and transferred to a separatory funnel and partitioned between DCM and water. The organic extracts were dried over $MgSO_4$, filtered and the solvent evaporated *in vacuo* to give the crude product as a yellow oil. The residue was purified by flash chromatography, 20% EtOAc/ light petroleum, to afford the product as a colourless solid (2.09 g, 5.6 mmol, 50%). Mp 84-86 °C; (Found: M^+, 373.1597. $C_{24}H_{24}NOP$ requires M^+, 373.1595); δ_H(270 MHz; $CDCl_3$) 0.69 (3H, d, J 6.8, CH_3), 0.79 (3H, d, *J* 6.8, CH_3), 1.44-1.49 (1H, m, C*H*$(CH_3)_2$), 3.83-3.87 (2H, m, CHN and CH_2O), 4.09-4.14 (1H, m, CH_2O), 6.84-6.88 (1H, m, Ar), 7.24-7.34 (12H, m, Ar), 7.89-7.91 (1H, m, Ar); δ_C(67.9 MHz; $CDCl_3$) 18.3 (CH_3), 18.9 (CH_3), 32.7 (*C*H $(CH_3)_2$),

70.0 (CH_2O), 73.0 (CHN), 127.9, 128.1, 128.3, 128.4, 128.5, 129.8, 129.8, 130.3, 133.5, 133.8, 134.1, 134.4 (Ar), 162.9 (C=N).

Identical to literature data.[85]

Synthesis of 1,3-diphenyl prop-2-en-1-ol 206



$C_{15}H_{14}O$
Exact Mass: 210.1045
Mol. Wt.: 210.2750
C, 85.68; H, 6.71; O, 7.61

Chalcone (20.0 g, 96.03 mmol, 1 equiv.) in MeOH (100 mL) along with $CeCl_3.7H_2O$ (35.78 g, 96.03 mmol, 1 equiv.) was cooled to −10 °C whilst sodium borohydride (3.68 g, 96.03 mmol, 1 equiv.) was added gradually over 15 min. After an hour the reaction was quenched with distilled water (80 mL) and extracted with dichloromethane (5 x 100 mL). The organic extracts were combined and dried over $MgSO_4$ and the solvent removed *in vacuo* to give the product as a colourless solid (19.82 g, 94.26 mmol, 98%). R_f 0.65 (40% EtOAc/ light petroleum); (Found M^+, 210.1045. $C_{15}H_{14}O$ requires M^+, 210.1044); ν_{max}(film)/cm^{-1} 3434 (O-H); δ_H(270 MHz; $CDCl_3$) 2.02 (1H, s, OH), 5.34 (1H, d, *J* 6.4, CH), 6.32-6.54 (2H, m, 2xCH), 7.22-7.44 (10H, m, Ar); δ_C(67.9 MHz; $CDCl_3$) 75.0, 126.3, 127.0, 127.6, 127.7, 128.5, 128.6, 130.2, 130.4, 130.4, 131.3, 131.5.

Identical to literature data.[132]

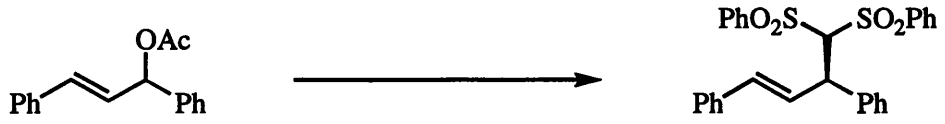
Synthesis of 1,3-diphenylprop-2-enyl acetate 59

$C_{17}H_{16}O_2$
Exact Mass: 252.1150
Mol. Wt.: 252.3122
C, 80.93; H, 6.39; O, 12.68

1,3-diphenyl prop-2-en-1-ol (19.82 g, 92.85 mmol, 1 equiv.) was dissolved in dichloromethane (265 mL) and DMAP (30 mg) was added to this mixture, followed by triethylamine (14.22 mL, 102.1 mmol, 1.1 equiv.) and acetic anhydride (10.1 mL, 10.93 g, 102.1 mmol, 1.1 equiv.). After stirring the solution at room temperature for two hours, it was washed with water (15 mL), 2M NaOH (15 mL), dried over $MgSO_4$ and filtered. The solvent was then evaporated *in vacuo* to give the product as a colourless oil (20.85 g, 82.63 mmol, 89%). R_f 0.68 (20% EtOAc/ light petroleum); (Found M^+, 252.1162. $C_{17}H_{16}O_2$ requires M^+, 252.1150); ν_{max}(film)/cm^{-1} 1737 (C=O); δ_H (270 MHz; $CDCl_3$) 2.12 (3H, s, Me), 6.33 (1H, dd, *J* 6.9, 15.6 Hz, C*H*CHPh, 6.44 (1H, d, *J* 6.9, C*H*OAc), 6.63 (1H, d, *J* 15.6, C*H*Ph), 7.19-7.43 (10H, m, Ar); δ_C (67.9MHz; $CDCl_3$) 21.3, 76.1, 126.6, 127.0, 127.4, 128.0, 128.1, 128.5, 128.6, 132.5, 136.1, 139.2, 170.0; *m/z* (EI) 252 (M^+, 10%), 210 (40), 192 (100), 115 (60), 77 (35).

Identical to literature data.[132]

Synthesis of (*S*)-[(1*E*)-3-phenyl-4,4-*bis*(phenylsulfonyl)-1-butenyl]benzene 209



$C_{28}H_{24}O_4S_2$
Exact Mass: 488.1116
Mol. Wt.: 488.6152
C, 68.83; H, 4.95; O, 13.10; S, 13.12

(4*S*)-2-(Fluorophenyl)-4-isopropyl-1,3-oxazoline (29 mg, 0.079 mmol, 5 mol%) and [{Pd ($\eta^3C_3H_5$)Cl}$_2$] (15 mg, 0.0395 mmol, 2.5 mol%) were heated at reflux in THF (1 mL) under N_2 for 2 h. Following this 1,3-diphenylprop-2-enyl acetate (0.4 g, 1.585 mmol, 1 equiv.) in 9 mL THF, N,O-*bis*(trimethylsilyl)acetamide (2.78 mL, 0.645g, 3.170 mmol, 2 equiv.), anhydrous caesium acetate (10 mg) and *bis*(phenylsulfonyl)methane (0.516 g, 1.743 mmol, 1.1 equiv.) in 2 mL THF were added. The reaction was heated at reflux for 48 hours. After cooling to room temperature, the contents of the flask were diluted with dichloromethane and then washed with saturated aqueous ammonium chloride (20 mL). The combined extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure. Column chromatography (dichloromethane) of the residue afforded a colourless solid (0.29 g, 0.52 mmol, 33%), 80% ee $[\alpha]_D^{30}$ -5.3° (c=1.0, $CHCl_3$), (Lit.[241] (*R*)-**209** $[\alpha]_D^{25}$ +5.6° (c=1.0, $CHCl_3$); R_f 0.4 (DCM); mp 163-164 °C (Found (FAB$^+$) MH^+, 489.1199. $C_{24}H_{25}S_2O_4$ requires MH^+, 489.1149); ν_{max}(Nujol)/cm^{-1} 1331 and 1150; δ_H(400 MHz; $CDCl_3$) 4.71 (1H, dd, *J* 2.4 and 9.3, CH=CH-C*H*), 5.09 (1H, d, *J* 2.4, C*H*(SO_2Ph)$_2$), 6.20 (1H, d, *J* 15.6, C*H*=CH-CH), 6.88 (1H, dd, *J* 9.3 and 15.6, CH=C*H*-CH), 7.20-8.33 (18H, m, Ar), 8.04 (2H, m, Ar); δ_C(100.6 MHz; $CDCl_3$) 47.6, 89.1, 124. 2, 126.6, 127.3, 127.8, 128.2, 128.4, 128.7, 128.9, 128.9,

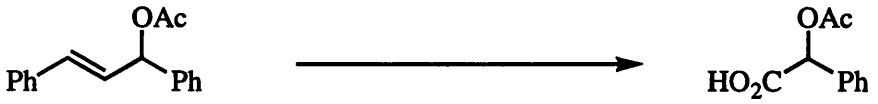
130.2, 134.0, 134.6, 134.9, 136.5, 137.9, 140.6, 140.6; *m/z* (FAB^+) 489 (MH^+, 50%), 346 (40), 205 (100), 193 (60).

Synthesis of 2-phenyl-3,3-*bis*(phenylsulfonyl)-1-propanoic acid 216

$C_{21}H_{18}O_6S_2$
Exact Mass: 430.0545
Mol. Wt.: 430.4896
C, 58.59; H, 4.21; O, 22.30; S, 14.89

A solution of (*S*)-[(1*E*)-3-phenyl-4,4-*bis*(phenylsulfonyl)-1-butenyl]benzene (0.244 g, 0.5 mmol, 1 equiv.) in MeOH (20 mL) and dichloromethane (20 mL) was ozonolised at –78 °C until the solution turned blue and TLC analysis showed no more starting material was present. Excess ozone was removed with oxygen (20 min). The reaction mixture was left to reach room temperature and the solvent was evaporated. The residue was treated with a solution of 90% formic acid 0.84 mL and 30% hydrogen peroxide (0.84 mL) and stirred overnight. The crude product was dissolved in dichloromethane (15 mL) and extracted with 1M NaOH (15 mL). The aqueous layer was acidified with HCl until the solution became pH 1. Following this the organic products were back-extracted using dichloromethane. The crude carboxylic acids were separated using column chromatography (5% acetic acid/DCM). The product was obtained as a colourless solid (0.015 g, 0.035 mmol, 7%) and benzoic acid was also formed (98%). R_f 0.63 (5% AcOH/ DCM); δ_H(270 MHz; $CDCl_3$) 4.55 (1H, d, *J* 11.0, C*H*$(SO_2Ph)_2$), 5.66 (1H, d, *J* 11.0, PhC*H*CO_2H), 7.01-8.06 (15H, m, Ar); δ_C(67.9 MHz; $CDCl_3$) 34.0, 84.7, 127.9, 128.5, 128.8, 129.1, 129.5, 130.4, 133.4, 134.5, 139.4, 139.6.

Synthesis of acetoxy-phenyl-acetic acid 218



$C_{10}H_{10}O_4$
Exact Mass: 194.0579
Mol. Wt.: 194.1866
C, 61.85; H, 5.19; O, 32.96

A solution of 1,3-diphenylprop-2-enyl acetate **59** (0.3 g, 1.19 mmol, 1 equiv.) in MeOH (8 mL) and DCM (18 mL) was ozonolised at –78 °C until the solution turned blue and TLC analysis showed no more starting material was present. Excess ozone was removed with oxygen (20 min). The reaction mixture was left to reach room temperature and the solvent was then evaporated. The residue was treated with a solution of 90% formic acid (1.98 mL) and 30% hydrogen peroxide (1.98 mL) and stirred overnight. Water (20 mL) was added to this solution and the product was extracted with dichloromethane (20 mL). The crude product was purified using column chromatography (5% Acetic acid/ DCM) to give the product as a yellow oil (0.102g, 0.525 mmol, 45%) and benzoic acid (0.143g, 99%) as a colourless solid. δ_H(270 MHz; $CDCl_3$) 2.19 (3H, s, Me), 5.93 (1H, s, C*H*CO_2H), 7.26-7.51 (5H, m, Ar); δ_C(67.9 MHz; $CDCl_3$) 20.7, 74.2, 127.6, 128.8, 129.4, 133.2, 170.5, 177.9.

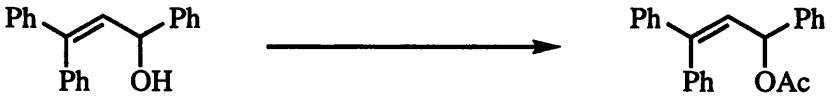
Synthesis of 3-phenyl-3-hydroxy-1,1-diphenylprop-1-ene 211

$C_{21}H_{18}O$
Exact Mass: 286.1358
Mol. Wt.: 286.3726
C, 88.08; H, 6.34; O, 5.59

Phenyl magnesium bromide (2.88 mL, 8.64 mmol, 1.2 equiv. 3M solution in ether) was added gradually to a stirring solution of β-phenyl cinnamaldehyde (1.5 g, 7.20 mmol, 1 equiv.) in THF (10 mL) whilst at 0 °C under N_2. Once the addition was complete, the reaction was warmed up to room temperature and stirred for an hour. It was quenched with saturated ammonium chloride solution (20 mL), extracted with ether (2x20 mL) and washed with water (15 mL). This was dried over $MgSO_4$, filtered and evaporated in *vacuo* to give the crude alcohol which was purified with column chromatography using 20% EtOAc/ light petroleum as the eluent. The product was obtained as a yellow oil (2.05 g, 7.16 mmol, 99%). R_f 0.5 (EtOAc/ light petroleum); (Found (EI) M^+, 286.1356. $C_{21}H_{18}O$ requires M^+ 286.1357); ν_{max}(film)/cm^{-1} 3300 (OH); δ_H(270 MHz; $CDCl_3$) 1.96 (1H, s, OH), 5.25 (1H, d, *J* 9.5, C*H*CHOH), 6.28 (1H, d, *J* 9.5, C*H*Ph) 7.22-7.40 (15H, m, Ar); *m/z* (EI) 286 (M^+, 25%), 268 (30), 178 (25), 167 (55), 105 (100), 84 (84).

Identical to literature data.[132]

1,3,3-triphenylprop-2-enyl acetate 132

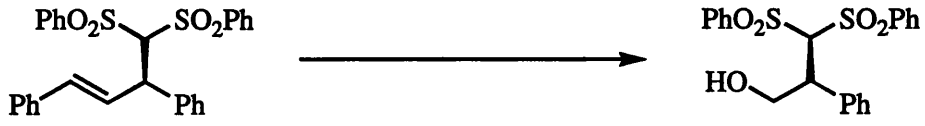


$C_{23}H_{20}O_2$
Exact Mass: 328.1463
Mol. Wt.: 328.4098
C, 84.12; H, 6.14; O, 9.74

The alcohol **211** (2.08 g, 7.26 mmol, 1 equiv.) was dissolved in dichloromethane (10 mL) and catalytic DMAP (~15mg) was added. After stirring at room temperature for 5 min, triethylamine (1.52 mL, 1.10 g, 10.93 mmol, 1.5 equiv.) was added along with acetic anhydride (1.03 mL, 10.93 mmol, 1.5 equiv.). After stirring the reaction for two hours, it was quenched with water (30 mL) and extracted with DCM. The organic extracts were combined and washed with 1M NaOH (2 x 30 mL) and water (30 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent evaporated in *vacuo*. The product was purified by column chromatography using 15% EtOAc/light petroleum as the eluent. The product was obtained as a colourless solid (2.04 g, 6.21 mmol, 88%). R_f 0.48 (15% EtOAc/ light petroleum), mp 69-71 °C; (Found (EI) MH^+, 328.1463); ν_{max}(Nujol)/cm^{-1} 1733 (C=O); δ_H(270MHz; $CDCl_3$) 2.04 (3H, s, Me), 6.30 (2H, m, 2xCH), 7.22-7.40 (15H, m, Ar); δ_C(67.9 MHz; $CDCl_3$) 21.3, 74.0, 126.1, 126.8, 127.4, 127.7, 127.8, 127.9, 128.1, 128.3, 128.5, 129.6, 138.7, 140.1, 141.2, 144.5, 169.6; *m/z* (FAB^+) 328 (M^+, 10%), 269 (100), 191 (20).

Identical to literature data.[132]

Synthesis of (*S*)-2-phenyl-3,3-*bis*(phenylsulfonyl)-1-propanol 228

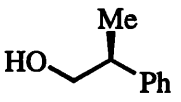


$C_{21}H_{20}O_5S_2$
Exact Mass: 416.0752
Mol. Wt.: 416.5060
C, 60.56; H, 4.84; O, 19.21; S, 15.39

The starting *bis*-sulfone (*S*)-**209** (1.06 g, 2.16 mmol, 1 equiv.) dissolved in MeOH (10 mL) and dichloromethane (45 mL) was cooled to –78 °C with O_2 gas bubbled through the solution for 5 min. Ozone was generated and bubbled through the reaction mixture until the reaction solution turned blue and TLC analysis revealed no more starting material was present. Oxygen was bubbled through the mixture again for 5 minutes and then sodium borohydride (0.164 g, 4.33 mmol, 2 equiv.) was added and the mixture was allowed to warm to room temperature overnight. The solvent was evaporated under reduced pressure and the crude product taken up in dichloromethane (80mL) and then washed with saturated ammonium chloride (50 mL), saturated brine (50 mL) and water (50 mL). The organic layer was dried ($MgSO_4$), filtered and solvent evaporated under reduced pressure. Column chromatography (65% ether/ light petroleum) of the residue afforded a colourless solid (0.803 g, 1.93 mmol, 89%), 80% ee $[\alpha]_D^{30}$ +80° (c=1.0, $CHCl_3$); R_f 0.19 (65% Ether/light petroleum); mp 75-76 °C; (Found (FAB$^+$) MH^+ 417.0819. $C_{21}H_{21}O_5S_2$ requires 417.0785); (Found: C, 61.0; H, 5.04. $C_{21}H_{20}O_5S_2$ requires C, 60.56; H, 4.84%); ν_{max}(Nujol)/cm^{-1} 3610 (OH); δ_H(270 MHz; $CDCl_3$) 2.28 (1H, s, OH), 4.05-4.09 (1H, m, CH), 4.32-4.41(2H, m, CH_2), 5.11 (1H, d, *J* 2.44, CH), 7.21-7.83 (15H, m, Ar); δ_C(67.9 MHz; $CDCl_3$) 47.8, 62.5, 86.1, 128.2,

129.1, 129.3, 129.4, 129.5, 129.6, 129.7, 134.7, 134.9, 137.6, 138.9, 140.1; *m/z* (FAB^+) 417 (MH^+, 100%), 399 (85), 245 (55).

Synthesis of (*S*)-2-phenyl-1-propanol 230



$C_9H_{12}O$
Exact Mass: 136.0888
Mol. Wt.: 136.1932
C, 79.37; H, 8.88; O, 11.75

Pre-activated (by stirring under N_2 overnight) magnesium turnings (0.4 g) were suspended in 18 mL of dry MeOH. The mixture was heated to 45-50 °C with stirring until gas evolution began (10 min) and the (*S*)-*bis*(sulfonyl)propanol **228** (0.25 g, 0.60 mmol) was added. The reaction was stirred overnight and more magnesium turnings were added if H_2 evolution ceased. At the end of the reaction the solution had a cloudy grey appearance. The solvent was evaporated *in vacuo* and dichloromethane (20 mL) added. The solution was poured into a mixture of 2M HCl and ice and then extracted with dichloromethane. The organic extracts were combined, dried ($MgSO_4$), filtered and the solvent evaporated in *vacuo*. The crude product was purified using column chromatography using 33% ether/light petroleum as the eluent. The product was obtained as a yellow oil (52 mg, 0.38 mmol, 65%). R_f 0.23 (33% Ether/light petroleum); (Found M^+, 136.0890. $C_9H_{12}O$ requires M^+, 136.888); ν_{max}(film)/cm^{-1} 3357 (OH); δ_H(270 MHz; $CDCl_3$) 1.27 (3H, d, *J* 7.0, CH_3), 2.92 (1H, septet, *J* 7.0, CH), 3.69 (2H, d, *J* 7.0, CH_2), 7.21-7.36 (5H, m, Ar); δ_C(67.9 MHz; $CDCl_3$) 17.5, 42.4, 68.6, 126.6, 127.5, 128.9, 143.7.

Identical to literature data.[214]

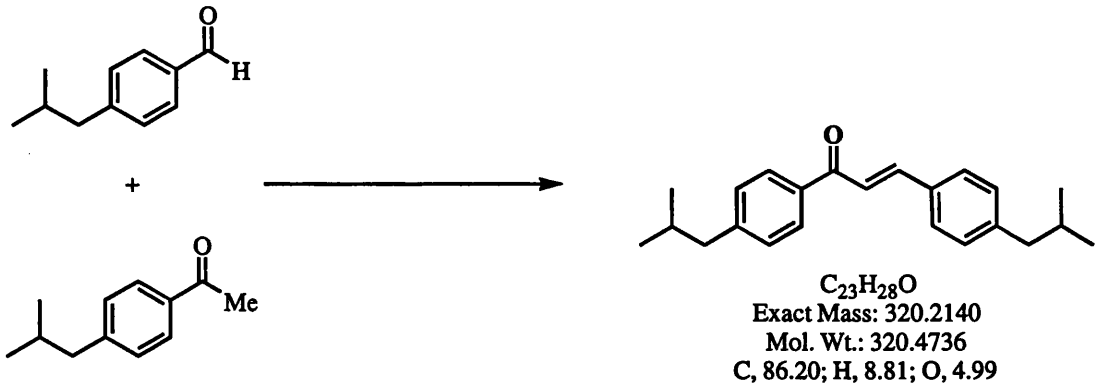
Synthesis of (*S*)-2-phenyl propanoic acid 231

$C_9H_{10}O_2$
Exact Mass: 150.0681
Mol. Wt.: 150.1768
C, 71.98; H, 6.71; O, 21.31

To a chromium trioxide (0.100 g, 1.0 mmol, 3.8 equiv.) solution in 1.5M H_2SO_4 (1.6 mL), was added 2-phenyl propanol (36 mg, 0.26 mmol, 1 equiv.), dissolved in acetone (3.3 mL) at 8 °C. The reaction was then stirred whilst allowing the temperature to reach room temperature. After stirring the reaction mixture overnight, it was diluted with ether (5 mL) and the organic layer washed with brine (2 x 5 mL). The organic layers were then combined and extracted with 1M NaOH (8 mL). The aqueous layer was acidified with H_2SO_4 and then extracted with ether. The organic layer was separated, dried ($MgSO_4$) filtered and the solvent evaporated. The product was obtained as a yellow oil (30 mg, 0.20 mmol, 77%). R_f 0.33 (ether/light petroleum); ν_{max}(film)/cm^{-1} 3030 (OH), 1704 (C=O); δ_H(270 MHz; $CDCl_3$) 1,49 (3H, d, *J* 7.0, Me), 3.69 (1H, q, *J* 7.0 and 14.3, CH), 7.24-7.32 (5H, m, Ar); δ_C(67.9 MHz; $CDCl_3$) 18.1, 45.3, 127.4, 127.6, 128.6, 132.6, 180.7.

Identical to literature data.[219]

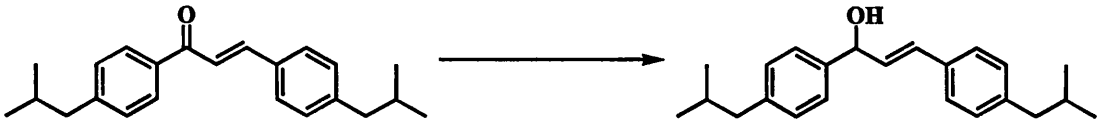
Synthesis of (2E)-1,3-*bis*(4-isobutylphenyl)-2-propen-1-one 234



$C_{23}H_{28}O$
Exact Mass: 320.2140
Mol. Wt.: 320.4736
C, 86.20; H, 8.81; O, 4.99

To a solution of 4-isobutylacetophenone (3.26 g, 18.49 mmol, 1 equiv.) and 4-isobutylbenzaldehyde (3.0 g, 18.49 mmol, 1 equiv.) in absolute ethanol (55 mL), either in a closed atmosphere or under N_2 at room temperature, was added a catalytic amount of NaOH (s) (2-3 pellets) and the mixture was vigorously stirred. The reaction was placed in an ice bath to initiate precipitation of product. The ice bath was then removed and the reaction carried out at room temperature. The reaction was left to stir for 24 h. Following this the product was filtered off, washed with cold ethanol, water and cold ethanol again, and dried in the *vacuum* oven to give a pale yellow powder (50-60%). R_f 0.57 (20% EtOAc/light petroleum); mp 62-65 °C; (Found M^+, 320.2129. $C_{23}H_{28}O$ requires M^+, 320.2140); (Found: C, 85.9; H, 8.82. $C_{23}H_{28}O$ requires C, 86.20; H, 8.81%); ν_{max}(film)/cm^{-1} 1661(C=O), 1596 (C=C); δ_H(270 MHz, $CDCl_3$) 0.91 (6H, d, *J* 6.6, CH_3), 0.92 (6H, d, *J* 6.6, CH_3), 1.86-1.94 (2H, m, 2xCH), 2.51 (2H, d, *J* 7.2, CH_2), 2.55 (2H, d, *J* 7.3, CH_2), 7.20 (2H, d, *J* 7.6, Ar), 7.27 (2H, d, *J* 7.8, Ar), 7.48-7.54 (1H, d, *J* 15.6, CH=CH), 7.54-7.58 (2H, d, *J* 8.1, Ar), 7.77-7.83 (1H, d, *J* 15.8, CH=CH), 7.9 (2H, d, *J* 8.2, Ar); δ_C(100.6 MHz, $CDCl_3$) 22.8, 30.5, 30.6, 45.7, 45.8, 121.5, 128.7, 128.9, 129.7, 130.1, 132.9, 136.5, 144.9, 145.2, 147.6, 190.5; *m/z* (EI) 320 (M^+, 30%), 263 (100), 161 (50).

Synthesis of (2*E*)-1,3-*bis*(4-isobutylphenyl)-2-propen-1-ol 235



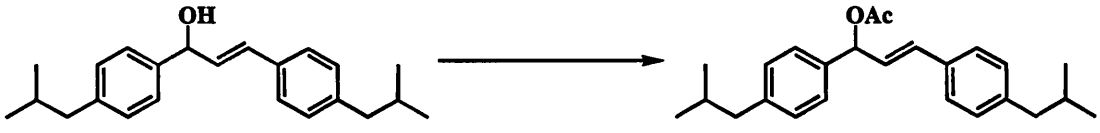
$C_{23}H_{30}O$
Exact Mass: 322.2297
Mol. Wt.: 322.4894
C, 85.66; H, 9.38; O, 4.96

The same procedure as that for 1,3-diphenyl prop-2-en-1-ol **206** was used.

The title compound was obtained as a pale yellow oil (5.85 g, 18.14 mmol, 95%). R_f 0.42 (20% EtOAc/light petroleum); (Found (EI) M^+, 322.2290. $C_{23}H_{30}O$ requires M^+, 322.2296); ν_{max}(film)/cm^{-1} 3356; δ_H(400 MHz; $CDCl_3$) 0.88 (6H, d, *J* 6.4, 2xCH_3), 0.89 (6H, d, *J* 6.7, 2xCH_3), 1.78-1.89 (2H, m, 2xCH), 2.03 (1H, s, OH), 2.44 (2H, d, *J* 7.6, CH_2), 2.46 (2H, d, *J* 7.6, CH_2), 5.33 (1H, d, *J* 6.6, CHOH), 6.31-6.37 (1H, dd, *J* 6.6, 15.9, CH=C*H*COH), 6.63-6.67 (1H, d, *J* 15.9, C*H*=CHCOH), 7.07 (2H, d, *J* 8.2, Ar), 7.13 (2H, d, *J* 7.9, Ar), 7.29 (2H, d, *J* 8.2, Ar), 7.32 (2H, d, *J* 7.9, Ar); δ_C(100.6 MHz; $CDCl_3$) 22.4, 30.2, 45.2, 75.1, 126.1, 126.4, 129.2, 129.3, 130.3, 130.7, 134.1, 140.2, 141.3, 141.5; *m/z* (EI) 322 (M^+, 12%), 279 (45), 161 (100), 91 (45), 43 (40).

Methylether **237** as a pale yellow oil. R_f 0.9 (20% EtOAc/light petroleum); δ_H(270 MHz; $CDCl_3$) 0.87 (6H, d, *J* 6.6, 2xCH_3), 0.89 (6H, d, *J* 6.6, 2xCH_3), 1.78-1.89 (2H, m, 2xCH), 2.43 (2H, d, *J* 5.7, CH_2), 2.45 (2H, d, *J* 6.9, CH_2), 3.36 (3H, s, OMe), 4.75 (1H, d, *J* 7.14, C*H*OMe), 6.24 (1H, dd, *J* 7.1, 15.7, CH=C*H*COMe), 6.59 (1H, d, *J* 15.7, C*H*=CHCOH), 7.07 (2H, d, *J* 8.1,Ar), 7.12 (2H, d, *J* 8.1, Ar), 7.28 (2H, d, *J* 7.9, Ar), 7.29 (2H, d, *J* 8.1, Ar); δ_C(67.9 MHz; $CDCl_3$) 22.3, 30.2, 45.1, 56.3, 84.3, 126.3, 126.5, 129.2, 129.3, 131.3, 134.1, 138.4, 141.1, 141.4.

Synthesis of (2*E*)-1,3-*bis*(4-isobutylphenyl)-2-propenyl acetate 236

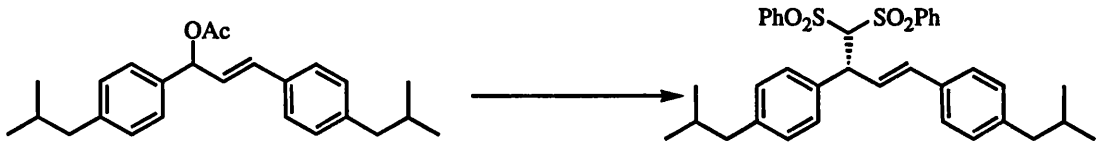


$C_{25}H_{32}O_2$
Exact Mass: 364.2402
Mol. Wt.: 364.5266
C, 82.37; H, 8.85; O, 8.78

The same procedure as that for 1,3-diphenylprop-2-enyl acetate **59** was used.

The title compound was obtained as a pale yellow oil (6.28 g, 17.23 mmol, 95%). R_f 0.65 (20% EtOAc/light petroleum); (Found (EI) M^+, 364.2394 $C_{23}H_{30}O$ requires M^+, 364.2402). (Found: C, 81.9; H, 8.71. $C_{23}H_{30}O$ requires C, 82.37; H, 8.71%); ν_{max}(film)/cm^{-1} 1739; δ_H(400 MHz; $CDCl_3$) 0.89 (6H, d, *J* 6.7, 2xCH_3), 0.87 (6H, d, *J* 6.7, 2xCH_3), 1.77-1.95 (2H, m, 2xCH), 2.11 (3H, s, OAc), 2.44 (2H, d, *J* 7.0, CH_2), 2.46 (2H, d, *J* 7.33, CH_2), 6.30 (1H, dd, *J* 7.0, 15.9, CH=C*H*COAc), 6.41 (1H, d, *J* 7.3, C*H*OAc), 6.61 (1H, d, *J* 15.9, C*H*=CHCH), 7.07 (2H, d, *J* 8.2, Ar), 7.13 (2H, d, *J* 7.9, Ar), 7.29 (2H, d, *J* 7.9, Ar), 7.30 (2H, d, *J* 7.6, Ar); δ_C(100.6 MHz; $CDCl_3$) 21.8, 22.7, 22.8, 30.6, 45.5, 76.6, 126.9, 127.1, 127.3, 129.7, 132.8, 134.1, 137.0, 142.1, 142.2, 170.5; *m/z* (EI) 364 (M^+, 10%), 304 (25), 261 (65), 43 (100).

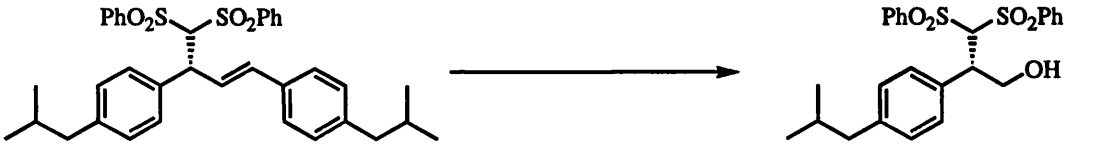
Synthesis of (*S*)-1-isobutyl-4-[(1*E*)-3-(4-isobutylphenyl)-4,4-*bis*(phenylsulfonyl)-1-butenyl]benzene 237



$C_{36}H_{40}O_4S_2$
Exact Mass: 600.2368
Mol. Wt.: 600.8296
C, 71.97; H, 6.71; O, 10.65; S, 10.67

The same procedure as that for *bis*-sulfone **209** was employed. Title compound was obtained as a colourless solid (5.20 g, 8.66 mmol, 79%), 79% ee $[\alpha]_D^{30}$ +18.66° (c=1.5, $CHCl_3$); mp 119-122 °C; R_f 0.47 in 20% EtOAc/light petroleum; (Found (FAB$^+$) MH^+, 601.2438. $C_{36}H_{41}O_4S_2$ requires MH^+, 601.2446); (Found: C, 71.9; H, 6.88. $C_{36}H_{40}O_4S_2$ requires C, 71.97; H, 6.71%); ν_{max}(film)/cm^{-1} 1320, 1154 (S=O), 1145 (S=O); δ_H(400 MHz; $CDCl_3$) 0.89 (6H, d, *J* 6.3, 2xCH_3), 0.90 (6H, d, *J* 6.8, 2xCH_3), 1.79-1.88 (2H, m, 2xCH), 2.42 (2H, d, *J* 6.8, CH_2), 2.45 (2H, d, *J* 6.8, CH_2), 4.66 (1H, dd, *J* 2.4, 9.3, CH=CH-C*H*), 5.08 (1H, d, *J* 2.4, C*H*($SO_2Ph)_2$), 6.17 (1H, d, *J* 15.8, C*H*=CH-CH), 6.81 (1H, dd, *J* 9.3, 15.8, CH=C*H*-CH), 7.01 (2H, d, *J* 8.3, Ar), 7.05 (2H, d, *J* 8.3, Ar), 7.18 (2H, d, *J* 7.8, Ar), 7.19 (2H, d, *J* 7.8, Ar), 7.35-8.02 (10H, m, CH(SO_2*Ph*)$_2$); δ_C(100.6 MHz; $CDCl_3$) 22.3, 30.1, 30.2, 44.9, 45.1, 47.3, 89.3, 123.4, 126.4, 127.9, 128.7, 128.9, 128.8, 129.2, 129.3, 130.3, 133.9, 134.0, 134.4, 134.7, 137.9, 138.0, 140.7, 141.4; *m/z* (CI) 600 (M^+, 10%), 318 (60), 305 (50), 142 (100).

Synthesis of (*S*)-2-(4-isobutylphenyl)-3,3-*bis*(phenylsulfonyl)-1-propanol 238



$C_{25}H_{28}O_5S_2$
Exact Mass: 472.1378
Mol. Wt.: 472.6132
C, 63.54; H, 5.97; O, 16.93; S, 13.57

The same procedure as that for 2-phenyl-3,3-*bis*(phenylsulfonyl)-1-propanol was employed. Title compound obtained as a colourless solid (1.30 g, 2.75 mmol, 83%), 79% ee $[\alpha]_D^{30}$ 57.5° (c=0.4, $CHCl_3$); R_f 0.05 (20% EtOAc/light petroleum); (Found (FAB$^+$) MH^+, 473.1447. $C_{25}H_{29}O_5S_2$ requires MH^+ 473.1411); (Found: C, 63.6; H, 6.11. $C_{25}H_{28}O_5S_2$ requires C, 63.54; H, 5.97%); δ_H(270 MHz; $CDCl_3$) 0.89 (6H, d, *J* 6.6, $CH(CH_3)_2$), 1.77-1.87 (1H, m, $CH(CH_3)_2$), 2.42 (2H, d, *J* 7.1, $CH_2CH(CH_3)_2$, 4.06 (1H, td, *J* 7.2, 2.4, $CHCH(SO_2Ph)_2$), 4.29 (1H, dd, *J* 7.0, 11.2, CH_2OH), 4.40 (1H, dd, *J* 7.3, 11.3, CH_2OH), 5.12 (1H, d, *J* 2.38, $CH(SO_2Ph)_2$), 7.01 (2H, d, *J* 8.2, Ar), 7.17 (2H, d, *J* 8.2, Ar), 7.39-7.81 (10H, m, $CH(SO_2Ph)_2$); δ_C(67.9 MHz; $CDCl_3$) 22.4, 30.0, 44.9, 47.1, 62.1, 86.0, 128.7, 128.9, 129.4, 134.2, 134.3, 138.5, 139.7, 141.2; *m/z* (CI) 473 (MH^+, 30%), 455 (100), 161 (70).

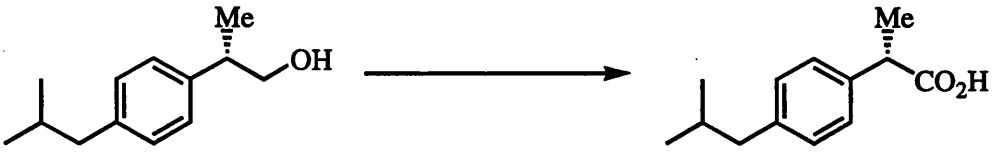
Synthesis of (*S*)-2-(4-isobutylphenyl)-1-propanol 239

$C_{13}H_{20}O$
Exact Mass: 192.1514
Mol. Wt.: 192.3004
C, 81.20; H, 10.48; O, 8.32

The same procedure as that for 2-phenyl-1-propanol was employed. Title compound was obtained as a colourless oil (0.41 g, 0.87 mmol, 81% isolated, 100% conversion by ^{1}H NMR), 79% ee; $[\alpha]_D^{30}$ –8.96° (c=1.45, $CHCl_3$), (Lit.[221b] $[\alpha]_D^{20}$ –14.8° (c=1.6, $CHCl_3$); ν_{max}/cm^{-1} 3380; δ_H(400 MHz, $CDCl_3$) 0.90 (6H, d, *J* 6.7, $CH(CH_3)_2$, 1.26 (3H, d, *J* 7.0, Me), 1.60 (1H, s, OH), 1.79-1.90 (1H, m, $CH(CH_3)_2$), 2.45 (2H, d, *J* 7.3, $CH_2CH(CH_3)_2$), 2.91 (1H, qt, CHMe), 3.69 (2H, d, *J* 6.9, CH_2OH), 7.10 (2H, d, *J* 8.3, Ar), 7.15 (2H, d, *J* 8.3, Ar); δ_C(100.6 MHz, $CDCl_3$) 18.0, 22.8, 30.6, 42.4, 45.4, 69.1, 126.1, 127.4, 129.5, 140.9.

Identical to literature data.[221]

Synthesis of Ibuprofen 197



$C_{13}H_{18}O_2$
Exact Mass: 206.1307
Mol. Wt.: 206.2840
C, 75.69; H, 8.79; O, 15.51

Pyridinium dichromate (1.01 g, 2.69 mmol, 5.18 equiv.) dissolved in anhydrous DMF (8 mL) was added to a solution of the alcohol, 2-(4-isobutylphenyl)-1-

propanol (0.1 g, 0.52 mmol, 1 equiv.) in DMF (2 mL). The reaction was then stirred under an inert atmosphere at room temperature for 12 h. The resulting mixture was poured into saturated aqueous sodium bisulfite (30 mL) and acidified to pH 1 with concentrated hydrochloric acid. Sodium chloride was added to make a saturated solution, which was extracted with ether (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure. Purification by column chromatography on silica using 40% EtOAc/ light petroleum as eluent gave Ibuprofen as a colourless solid (0.08 g, 0.40 mmol, 77%). mp 49-51 °C (lit. mp 50-52 °C); ν_{max}/cm^{-1} 3500 (O-H), 1710 (C=O); (1H, m, C*H*$(CH_3)_2$), 2.37 (2H, d, *J* 7.2, C*H*$_2$CH$(CH_3)_2$), 3.64 (1H, q, *J* 7.2, δ_H(270 MHz; $CDCl_3$) 0.82 (6H, d, *J* 6.6, CH(C*H*$_3)_2$), 1.43 (3H, d, *J* 7.1, Me), 1.75 (1H, m, C*H*$(CH_3)_2$), 2.37 (2H, d, *J* 7.2, C*H*$_2$CH$(CH_3)_2$), 3.64 (1H, q, *J* 7.2, C*H*Me), 7.02 (2H, d, *J* 8.1, Ar), 7.15 (2H, d, *J* 8.1, Ar).

Identical to literature data.[223]

Synthesis of 6-methoxy-2-napthaldehyde 245

$C_{12}H_{10}O_2$
Exact Mass: 186.0681
Mol. Wt.: 186.2098
C, 77.40; H, 5.41; O, 17.18

Into a flame-dried 2-necked round-bottomed flask, cooled under argon was placed 6-methoxy-2-bromonapthalene (3.0 g, 12.65 mmol, 1 equiv.) and anhydrous ether (65 mL). The resulting suspension was cooled to –78 °C and *n*-BuLi (9.88 mL, 15.81 mmol of 1.6M solution in hexane, 1.25 equiv.) was added. The reaction was then warmed up to room temperature and stirring was continued under argon for 1

h during which time the solid dissolved completely and the solution became light yellow. It was then cooled to –78 °C and N,N-dimethylformamide (2.45 mL, 31.62 mmol, 2.5 equiv.) was added. On addition of N,N-dimethylformamide, the solution turned white opaque. The cold bath was removed, and stirring was continued for 2 h, after which period the reaction was quenched with water and extracted with ether. The organic layers were combined and washed with water, dried over $MgSO_4$, filtered and the solvent evaporated *in vacuo*. Purification by column chromatography on silica using 15% EtOAc/light petroleum as eluent gave **245** as a colourless solid (2.17g, 11.65 mmol, 93%). Mp 81-83 °C (lit. mp 82-83 °C); δ_H (270 MHz; $CDCl_3$) 3.93 (3H, s, OMe), 7.14-7.22 (2H, m, Ar), 7.76 (1H, d, *J* 8.5, Ar), 7.80-7.89 (2H, m, Ar), 8.21(1H, s, Ar), 10.05(1H, s, CHO); δ_C (67.9 MHz; $CDCl_3$) 55.5, 106.1, 119.9, 123.6, 127.7, 127.9, 131.1, 132.2, 134.2, 138.3, 160.3, 192.0.

Identical to literature data.[226]

Synthesis of 1-(6-methoxy-2-napthyl)-ethanol 246

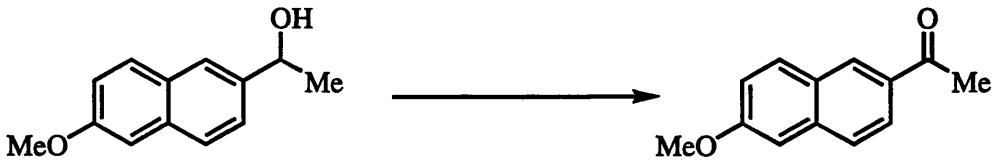
$C_{13}H_{14}O_2$
Exact Mass: 202.0994
Mol. Wt.: 202.2524
C, 77.20; H, 6.98; O, 15.82

Into a flame-dried 2-necked round-bottomed flask, cooled under argon was placed 6-methoxy-2-bromonapthalene (6.0 g, 25.30 mmol, 1 equiv.) and anhydrous ether (200 mL) added. The resulting suspension was cooled to –78 °C and *n*-BuLi (12.65 mL, 30.36 mmol of 2.4 M solution in hexane, 1.2 equiv.) was added. The

reaction was then warmed up to room temperature and stirring was continued under argon for 1 h during which time the solid dissolved completely and the solution became light yellow. It was then cooled to –78 °C and (3.54 mL, 63.25 mmol, 2.5 equiv.) of acetaldehyde was added. The cold bath was removed, and stirring was continued for 2 h, by which time the solution turned opaque orange. The reaction was quenched with water and extracted with ether. The organic layers were combined and washed with water, dried over $MgSO_4$, filtered and the solvent evaporated in vacuo. Purification by column chromatography on silica using 30% EtOAc/ light petroleum as eluent gave **246** as a pale yellow solid (4.40 g, 21.75 mmol, 86%). Rf 0.23 (20% EtOAc/ light petroleum); δ_H (400 MHz; $CDCl_3$) 1.20 (3H, d, *J* 6.4, CH_3), 3.91 (3H, s, OMe), 5.03 (1H, q, 6.4, C*H*Me), 7.13 (1H, s, Ar), 7.17 (1H, d, *J* 2.6, Ar), 7.47 (1H, dd, *J* 1.6, 8.5, Ar), 7.70-7.75 (3H, m, Ar); δ_C(67.9 MHz; $CDCl_3$) 25.0, 55.3, 70.5, 105.6, 118.9, 123.7, 124.3, 127.1, 128.7, 129.4, 134.4, 140.9, 157.6.

Identical to literature data.[226]

Synthesis of 6-acetyl-2-methoxynapthalene 243



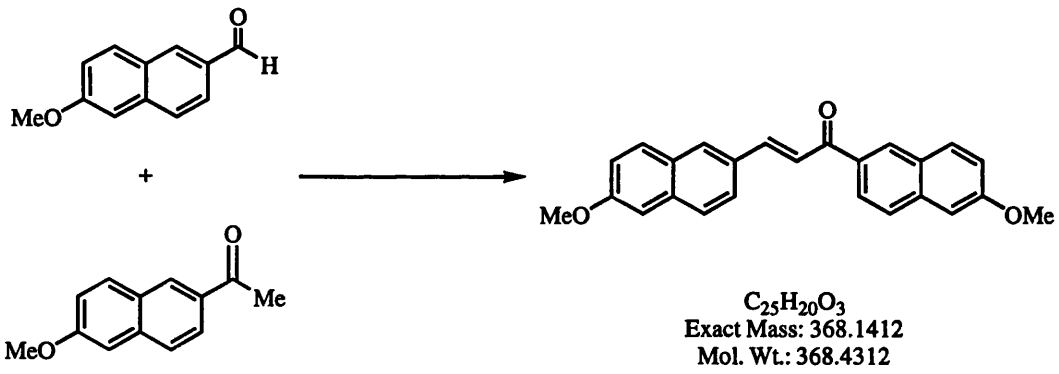
$C_{13}H_{12}O_2$
Exact Mass: 200.0837
Mol. Wt.: 200.2366
C, 77.98; H, 6.04; O, 15.98

DDQ (2.30 g, 10.17 mmol) was added to a solution of 1-(6-methoxy-2-napthyl)-ethanol (2.06 g, 10.17 mmol) in THF (60 mL) at room temperature. The reaction mixture immediately turned greenish brown (exothermic reaction) and $DDQH_2$

started to precipitate. The reaction was stirred overnight. It was then quenched with water and extracted with DCM. The DCM layer was washed with 1M NaOH (3 x 200 mL), followed by water. It was dried over $NaSO_4$, filtered and the solvent evaporated under *vacuum*. The product was filtered through a small pad of silica to give 243 as a colourless flaky solid (1.88g, 9.39 mmol, 92%); mp 103-105 °C (lit. 104-105 °C); $\nu_{max}(CHCl_3)/cm^{-1}$ 1690; δ_H(270 MHz; $CDCl_3$) 2.68 (3H, s, Me), 3.93 (3H, s, OMe), 7.13 (1H, d, Ar), 7.17 (1H, d, Ar), 7.19 (1H, d, Ar), 7.23 (1H, s, Ar), 7.74 (1H, d, *J* 8.6, Ar), 7.82 (1H, d, *J* 8.9, Ar), 7.99 (1H, d, Ar), 8.36 (1H, s, Ar).

Identical to literature data.[226]

Synthesis of (2*E*)-1,3-*bis*(6-methoxy-2-napthyl)-2-propen-1-one 247

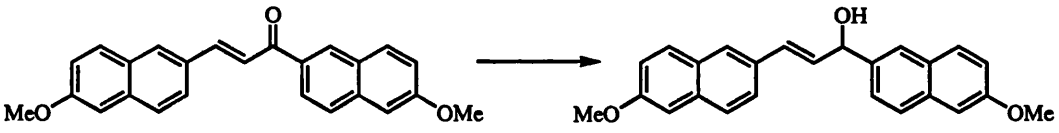


$C_{25}H_{20}O_3$
Exact Mass: 368.1412
Mol. Wt.: 368.4312
C, 81.50; H, 5.47; O, 13.03

To a solution of 2-(6-methoxynapthyl)methylketone (6.79 g, 33.95 mmol, 1 equiv.) and 6-methoxy-2-napthaldehyde (6.31 g, 33.95 mmol, 1 equiv.) in absolute ethanol (900 mL), either in a closed atmosphere or under N_2 at room temperature, was added a catalytic amount of NaOH (s) (2-3 pellets) and the mixture was vigorously stirred at room temperature. Within one hour the product started to precipitate. The reaction was left to stir for 24 h. Following this the product was filtered off, washed with cold ethanol water and cold ethanol again,

and dried in the *vacuum* oven to give a pale yellow powder (80-96 %) obtained as a very pale yellow powder. R_f 0.25 (35% Et_2O/light petroleum); (Found (EI) M^+ 368.1410. $C_{25}H_{20}O_3$ requires M^+ 368.1412); (Found: C, 81.5; H, 5.42. $C_{25}H_{20}O_3$ requires C, 80.6; H, 5.47%); ν_{max}/ cm^{-1}1658 (C=C), 1620 (C=O), 1585 (C=C, Ar), 1266 (C-O), 1166 (C-O); δ_H(400 MHz; $CDCl_3$) 3.94 (3H, s, OMe), 3.96 (3H, s, OMe), 7.15-7.25 (5H, m, CH=CH and 3Ar), 7.74-8.52 (9H, m, Ar); δ_C (100.6 MHz; $CDCl_3$) 55.4, 55.4, 105.8, 106.0, 119.5, 119.7, 121.0, 124.5, 125.3, 127.2, 127.5, 127.9, 128.8, 129.8, 130.2, 130.4, 131.1, 133.7, 135.8, 137.1, 144.7, 158.9, 159.7, 189.8; *m/z* (EI) 368 (M^+, 75%), 185 (100), 157 (45).

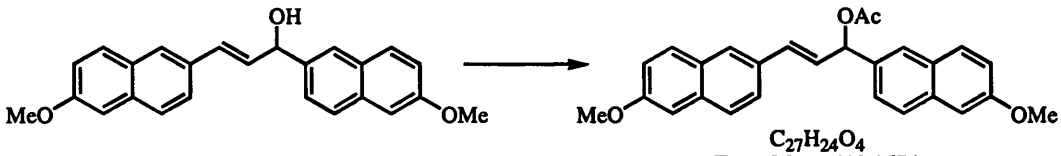
Synthesis of (2*E*)-1,3-*bis*(6-methoxy-2-napthyl)-2-propen-1-ol 248



$C_{25}H_{22}O_3$
Exact Mass: 370.1569
Mol. Wt.: 370.4470
C, 81.06; H, 5.99; O, 12.96

The same procedure as that for 1,3-diphenyl prop-2-en-1-ol **206** was employed. Title compound was obtained as a very pale yellow powder. (Found (EI) M^+ 370.1557 $C_{25}H_{22}O_3$ requires M^+ 370.1568); δ_H(270 MHz; DMSO) 3.85 (3H, s, OMe), 3.86 (3H, s, OMe), 5.75 (1H, d, *J* 4.6, C*H*OH), 6.5 (1H, dd, *J* 6.2, 15.9, CH=C*H*CHOH), 6.78 (1H, d, *J* 15.9, C*H*=CHCHOH), 7.11-7.89 (12H, m, Ar); δ_C(67.9 MHz; DMSO) 55.2, 73.5, 105.9, 106.0, 118.6, 118.8, 124.3, 125.6, 125.9, 126.7, 127.1, 128.4, 128.5, 128.6, 129.3, 129.4, 132.0, 133.2, 133.6, 133.8, 139.7, 157.1, 157.3; *m/z* (EI) 370 (M^+, 8%), 354 (20), 185 (25), 57 (100).

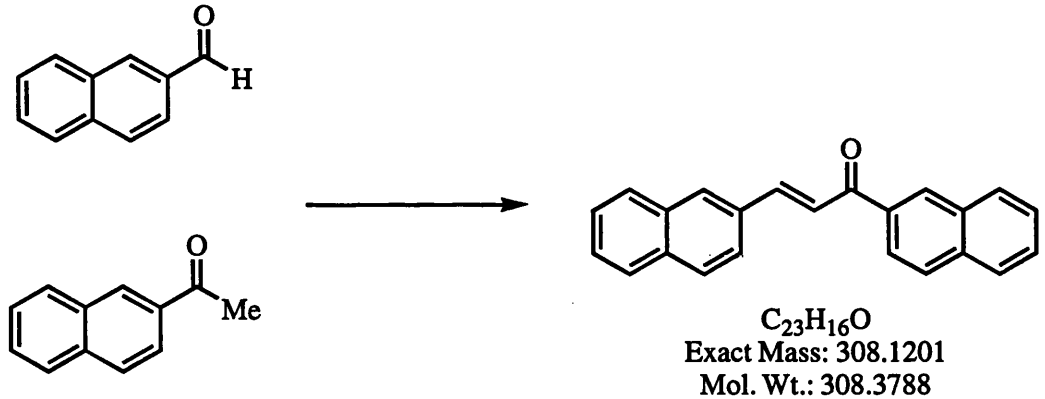
Synthesis of (2*E*)-1,3-*bis*(6-methoxy-2-napthyl)-2-propenyl acetate 251



$C_{27}H_{24}O_4$
Exact Mass: 412.1674
Mol. Wt.: 412.4842
C, 78.62; H, 5.86; O, 15.52

The same procedure as that for 1,3-diphenylprop-2-enyl acetate **59** was used. Title compound was obtained as a colourless oil. δ_H(400 MHz;$CDCl_3$) 2.17 (3H, s, OAc), 3.90 (3H, s, OMe), 3.91 (3H, s, OMe), 6.50 (1H, dd, *J* 6.8, *J* 15.6, CH=C*H*COAc), 6.62 (1H, d, *J* 6.8, C*H*OAc), 6.77 (1H, d, *J* 15.6, C*H*=CHCOAc), 7.08-7.17 (4H, m, Ar), 7.49-7.83 (8H, m, Ar); δ_C(100.6 MHz; $CDCl_3$) 21.9, 55.6, 76.8, 105.9, 106.1, 119.3, 119.4, 124.4, 125.7, 126.3, 127.0, 127.1, 127.3, 127.5, 128.9, 129.0, 129.7, 129.8, 131.8, 133.0, 134.6, 158.0, 158.1, 170.2.

Synthesis of 1,3-di-naphthalen-2-yl-propenone 253



$C_{23}H_{16}O$
Exact Mass: 308.1201
Mol. Wt.: 308.3788
C, 89.58; H, 5.23; O, 5.19

To a solution of 2-acetonapthone (4.0 g, 23.50 mmol, 1 equiv.) and 2-napthaldehyde (3.67 g, 23.50 mmol, 1 equiv.) in absolute ethanol (40 mL), either in a closed atmosphere or under N_2 at room temperature, was added a catalytic amount of NaOH (s) (2-3 pellets) and the mixture was vigorously stirred. The

reaction was cooled with an ice bath to initiate precipitation of the product. After 5 min product started to precipitate and the ice bath was removed. The reaction was left to stir for 24 h at r.t. Following this the product was filtered off, washed with cold ethanol water and cold ethanol again, and dried in the *vacuum* oven to give a pale yellow powder (7.17 g, 23.26 mmol, 99 %) obtained as a yellow powder. mp 199-200 °C (lit. 199-200 °C); ν_{max}(film)/ cm^{-1}1662 (C=C), 1626 (C=O); δ_H(400 MHz; $CDCl_3$) 3.94 (3H, s, OMe), 3.96 (3H, s, OMe), 7.15-7.25 (5H, m, CH=CH and 3Ar), 7.74-8.52 (9H, m, Ar). δ_C(75.4 MHz; $CDCl_3$) 122.7, 124.3, 125.1, 127.4, 127.9, 128.4, 128.4, 129.0, 129.2, 129.2, 129.3, 130.11, 130.5, 131.3, 133.0, 133.1, 136.1, 136.2, 145.5, 190.9; *m/z* (CI) 308 (M^+, 100%), 180 (20), 154 (55), 140 (15), 127 (25).

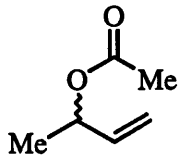
Experimental for Chapter 2

General procedure (1) for the preparation of allylic acetates from the corresponding alcohols.

The allylic acetates used throughout this chapter were either purchased or prepared from the corresponding alcohols by the following procedure. These are well known compounds and were therefore characterised by ^{1}H NMR data and by comparison with literature values. ^{1}H NMR data is given for reference purposes.

A 100 mL round-bottomed flask was charged with a stirring bead and the starting alcohol (4.99 g, 69.23 mmol, 1 equiv.). HPLC grade DCM was then added (60 mL), along with a microspatula of DMAP. It was then stoppered and flushed with nitrogen and the reaction vessel was cooled to 0 °C. Triethylamine (10.58 mL, 7.70 g, 76.15 mmol, 1.1 equiv.) was added *via* a syringe. After stirring for 5 min, acetic anhydride (13.0 mL, 14.06 g, 138.46 mmol, 2 equiv.) was added also *via* a syringe. The reaction was stirred at room temperature until TLC analysis showed complete consumption of the starting alcohol. This is typically about four hours. The reactions were then diluted with DCM and washed with 2x 2M NaOH, 0.5M HCl and finally water. The organic layer was then dried over $NaSO_4$, filtered and the solvent evaporated. Butenyl acetates were handled more carefully since these compounds are volatile. Column chromatography of these allylic acetates resulted in decomposition. Therefore the acetates were either purified via distillation or used without further purification.

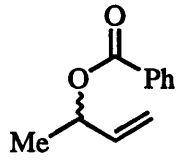
But-2-enyl acetate



R_f ~ 0.7 (30% Et_2O/light petroleum); δ_H(400 MHz; $CDCl_3$) 1.25 (3H, d, *J* 6.6, CH_3CH), 2.20 (3H, s, CO_2Me), 5.07 (1H, dt, *J* 10.5, 1.4, HC=C*H*H), 5.28 (1H, m, HC=CH*H*), 5.78 (1H, ddd, *J* 5.9, 10.5, 17.4, C*H*=CHH).

Identical to literature data.[244]

Benzoic acid 1-methyl-allyl ester



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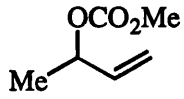
R_f ~ 0.6 (15% Et_2O/light petroleum); δ_H(400 MHz; $CDCl_3$) 1.45 (3H, d, *J* 6.6, CH_3CH), 5.19 (1H, dd, *J* 1.2, 10.5, HC=C*H*H), 5.33 (1H, dd, *J* 1.2, 17.2 HC=CH*H*), 5.96 (1H, ddd, *J* 5.5, 10.5, 17.2, C*H*=CHH), 7.44 (2H, dd, *J* 0.8, 7.5, Ar), 7.55 (1H, dd, *J*, 7.3, 7.4, Ar), 8.06 (2H, dd, *J* 1.5, 8.2, Ar).

Identical to literature data.[245]

(*E*)-But-2-enyl methyl carbonate 283



283

A flame dried round-bottomed flask was charged with 1-butene-3-ol (1.20 mL, 1.0 g, 13.86 mmol, 1 equiv.) and pyridine (15 mL) added. The solution was cooled to 0 °C and methyl chloroformate (1.18 mL, 15.25 mmol, 1.1 equiv.) was added dropwise. The reaction mixture was stirred overnight. Then the solution was poured into a mixture of crushed ice and 2M HCl and stirred until the ice was completely dissolved. The mixture was extracted three times with DCM. It was washed with $CuSO_4$ (2 x 30 mL) followed by water, dried over $NaSO_4$, filtered and evaporated. The crude compound was purified by silica gel column chromatography using (10% Et_2O/ light petroleum) to give the title compound as a colourless liquid. R_f 0.31 (10% Et_2O/ light petroleum); δ_H(300 MHz; $CDCl_3$) 1.34 (3H, d, *J* 6.5, Me), 3.74 (3H, s, CO_2Me), 5.28-5.13 (3H, m), 5.85 (1H, ddd, *J* 6.4, 10.6, 17.2, CH=).

Identical to literature data.[229]

General procedure (1) for the palladium catalysed allylic substitution of but-2-enyl acetate with soft carbon nucleophiles in the presence of monophosphine ligands.

Into an evacuated round-bottomed flask containing a stirring bead, were placed $[(C_3H_5)PdCl]_2$ (0.008 g, 0.0219 mmol, 2.5 mol%) and Cy_3P (0.0245 g, 0.0876 mmol, 10 mol%). The flask was flushed with nitrogen and dry THF (2 mL) was added. The pale yellow solution was stirred for 10 min, before the addition of but-

2-enyl acetate (0.1 g, 0.876 mmol, 1 equiv.). This solution was then added into a solution of the nucleophile generated *in situ* from the appropriate malonate (1.31 mmol, 1.5 equiv.) and NaH (0.058 g (60% in mineral oil), 1.45 mmol, 1.1 equiv. to malonate), in THF (10 mL). The reaction mixture was stirred at room temperature until no more starting material was observed by GC. The reaction was quenched by passing the solution through a small pad of silica. (Any sample of the reaction mixture analysed by GC was also subjected to this treatment.) The ratio of branched to linear products was determined by GC and by ^{1}H NMR. The products were purified by silica gel column chromatography.

Alternative procedure.

Into an evacuated round-bottomed flask containing a stirring bead, were placed $[(C_3H_5)PdCl]_2$ (0.008 g, 0.0219 mmol, 2.5 mol%) and Cy_3P (0.0245 g, 0.0876 mmol, 10 mol%). The flask was flushed with nitrogen and dry THF (2 mL) was added. The pale yellow solution was stirred for 10 min, before the addition of but-2-enyl acetate (0.1 g, 0.876 mmol, 1 equiv.). This solution was then added into a solution of the nucleophile generated *in situ* from the appropriate malonate (1.31 mmol, 1.5 equiv.) and KH (0.18 g, 30-35% w/w in mineral oil, 1.45 mmol, 1.1 equiv. to malonate) in THF (10 mL). The reaction mixture was stirred at room temperature until no more starting material was observed by GC. The reaction was quenched by passing the solution through a small pad of silica. (Any sample of the reaction mixture analysed by GC was also subjected to this treatment.) The ratio of branched to linear products was determined by GC and by ^{1}H NMR. The products were purified by silica gel column chromatography.

Alternative procedure.

Into an evacuated round-bottomed flask containing a stirring bead, were placed $[(C_3H_5)PdCl]_2$ (0.008 g, 0.0219 mmol, 2.5 mol%) and Cy_3P (0.0245 g, 0.0876 mmol, 10 mol%). The flask was flushed with nitrogen and dry DCM (2 mL) was added. The pale yellow solution was stirred for 10 min, before the addition of but-2-enyl acetate (0.1 g, 0.876 mmol, 1 equiv.). This solution was then added into a solution of the nucleophile generated *in situ* from the appropriate malonate (1.31 mmol, 1.5 equiv.) and DBU (0.21mL, 0.22 g, 1.45 mmol, 1.1 equiv. to malonate) in DCM (10 mL). This clear solution was stirred at room temperature until no more starting material was observed by GC. The reaction was quenched by passing the solution through a small pad of silica. (Any sample of the reaction mixture analysed by GC was also subjected to this treatment.) The ratio of branched to linear products was determined by GC and by ^1H NMR. The products were purified by silica gel column chromatography.

Alternative procedure.

Into an evacuated round-bottomed flask containing a stirring bead, were placed $[(C_3H_5)PdCl]_2$ (0.008 g, 0.0219 mmol, 2.5 mol%) and Cy_3P (0.0245 g, 0.0876 mmol, 10 mol%). The flask was flushed with nitrogen and dry DCM (2 mL) was added. The pale yellow solution was stirred for 10-15 min, before the addition of but-2-enyl acetate (0.1 g, 0.876 mmol, 1 equiv.). This solution was then added into a solution of the nucleophile generated *in situ* from the appropriate malonate (1.31 mmol, 1.5 equiv.), BSA (0.35mL, 1.45 mmol, 1.1 equiv. to malonate) and KOAc (catalytic- a microspatula full) in DCM (10 mL). The reaction mixture was stirred at room temperature until no more starting material was observed by GC.

The reaction was quenched by passing the solution through a small pad of silica. (Any sample of the reaction mixture analysed by GC was also subjected to this treatment.) The ratio of branched to linear products was determined by GC and by ^{1}H NMR. The products were purified by silica gel column chromatography.

General procedure (2) for the palladium catalysed allylic substitution of crotyl acetate with soft carbon nucleophiles in the presence of monophosphine ligands.

Into an evacuated round-bottomed flask containing a stirring bead, were placed $[(C_3H_5)PdCl]_2$ (0.008 g, 0.0219 mmol, 2.5 mol%) and Cy_3P (0.0245 g, 0.0876 mmol, 10 mol%). The flask was flushed with nitrogen and dry THF (2 mL) was added. The pale yellow solution was stirred for 10-15 min, before the addition of crotyl acetate (0.1 g, 0.876 mmol, 1 equiv.). This solution was then added into a solution of the nucleophile generated *in situ* from the appropriate malonate (1.31 mmol, 1.5 equiv.) and NaH (0.058 g (60% in mineral oil), 1.45 mmol, 1.1 equiv. to malonate), in THF (10 mL). The reaction mixture was stirred at room temperature until no more starting material was observed by GC. The reaction was quenched by passing the solution through a small pad of silica. (Any sample of the reaction mixture analysed by GC was also subjected to this treatment.) The ratio of branched to linear products was determined by GC and by ^{1}H NMR. The products were purified by silica gel column chromatography.

General procedure (3) for the palladium catalysed allylic substitution of but-2-enyl benzoate with soft carbon nucleophiles in the presence of monophosphine ligands.

Into an evacuated round-bottomed flask containing a stirring bead, were placed $[(C_3H_5)PdCl]_2$ (0.031 g, 0.085 mmol, 2.5 mol%) and Cy_3P (0.095 g, 0.34 mmol, 10 mol%). The flask was flushed with nitrogen and dry THF (4 mL) was added. The pale yellow solution was stirred for 10-15 min, before the addition of but-2-enyl benzoate (0.6 g, 3.40 mmol, 1 equiv.). This mixture was then added into a solution of the nucleophile generated *in situ* from dimetyl malonate (0.58mL, 5.1 mmol, 1.5 equiv.) and NaH (0.23g (60% in mineral oil), 5.61 mmol, 1.1 equiv. to malonate) in THF (20 mL). The reaction mixture was stirred at room temperature until no more starting material was observed by GC. The reaction was quenched by passing the solution through a small pad of silica. (Any sample of the reaction mixture analysed by GC was also subjected to this treatment.) The ratio of branched to linear products was determined by GC and by ^1H NMR. The products were purified by silica gel column chromatography.

General procedure (4) for the palladium catalysed allylic substitution of (*E*)-But-2-enyl methyl carbonate with soft carbon nucleophiles in the presence of monophosphine ligands.

Into an evacuated round-bottomed flask containing a stirring bead, were placed $[(C_3H_5)PdCl]_2$ (0.008 g, 0.0219 mmol, 2.5 mol%) and Cy_3P (0.0245 g, 0.0876 mmol, 10 mol%). The flask was flushed with nitrogen and dry THF (2 mL) was added. The pale yellow solution was stirred for 10-15 min, before the addition of (*E*)-But-2-enyl methyl carbonate (0.11 g, 0.876 mmol, 1 equiv.). This solution was then added into a solution of the nucleophile generated *in situ* from the appropriate malonate (1.31 mmol, 1.5 equiv.) and base (1.1 equiv. to malonate), in THF (10 mL). The reaction mixture was stirred at room temperature until no more

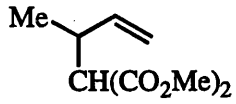
starting material was observed by GC. The clear yellow solution was quenched by passing it through a small pad of silica. (Any sample of the reaction mixture analysed by GC was also subjected to this treatment.) The ratio of branched to linear products was determined by GC and by ^{1}H NMR. The products were purified by silica gel column chromatography.

General procedure (5) for the palladium catalysed allylic substitution of 3-chloro-1-butene with soft carbon nucleophiles in the presence of monophosphine ligands.

Into an evacuated round-bottomed flask containing a stirring bead, were placed $[(C_3H_5)PdCl]_2$ (0.008 g, 0.0219 mmol, 2.5 mol%) and Cy_3P (0.0245 g, 0.0876 mmol, 10 mol%). The flask was flushed with nitrogen and dry THF (2 mL) was added. The pale yellow solution was stirred for 10 min, before the addition of 3-chloro-1-butene (0.088 mL, 0.079 g, 0.876 mmol, 1 equiv.). This solution was then added into a solution of the nucleophile generated *in situ* from dimethyl malonate (0.15 mL, 1.31 mmol, 1.5 equiv.) and NaH (0.058 g (60% w/w in mineral oil), 1.45 mmol, 1.1 equiv. to malonate), in THF (10 mL). The reaction mixture was stirred at room temperature overnight. The reaction was quenched by the addition of saturated ammonium chloride, extracted with DCM and the organic extracts were washed with brine and water and dried over $NaSO_4$, and the solvent was evaporated in vacuo. A sample was taken in a small amount of DCM and passed through a small pad of silica for GC analysis. The ratio of branched to linear products was determined by GC and by ^{1}H NMR. The product was purified by silica gel column chromatography.

Branched and linear regioisomeric products were not separable by column chromatography.

Dimethyl (1-methylprop-2-enyl)malonate 264



264

$C_9H_{14}O_4$
Exact Mass: 186.0892
Mol. Wt.: 186.2072
C, 58.05; H, 7.58; O, 34.37

Title compound was obtained as a colourless oil. R_f 0.3 (30% Et_2O/ light petroleum); ν_{max}/cm^{-1} 2956, 1737, 1644, 1566, 1436, 1268, 1199, 1154; δ_H(400 MHz; $CDCl_3$) 1.03 (3H, d, *J* 6.8, Me), 2.89 (1H, m, C*H*CH=CH_2), 3.24 (1H, d, *J* 9.0, C*H*($CO_2Me)_2$), 3.66 (3H, s, CO_2Me), 3.67 (3H, s, CO_2Me), 4.99 (2H, ddm, CH=CH_2), 5.70 (1H, ddd, C*H*=CH_2); δ_C(100.6 MHz; $CDCl_3$) 18.4, 38.5, 52.7, 52.8, 57.9,115.8, 139.8, 168.8, 168.8.

Identical to literature data.[246]

Dimethyl (but-2-enyl)malonate 265

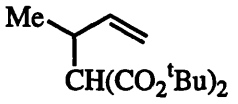
265

$C_9H_{14}O_4$
Exact Mass: 186.0892
Mol. Wt.: 186.2072
C, 58.05; H, 7.58; O, 34.37

Title compound was obtained as a colourless oil. R_f 0.3 (30% Et_2O/ light petroleum); δ_H(400 MHz; $CDCl_3$) 1.56 (3H, dd, Me), 2.50 (2H, dd, *J* 6.7, 7.5, CHC*H*$_2$), 3.34 (1H, t, *J* 7.7, C*H*($CO_2Me)_2$), 3.64 (6H, s, CO_2Me), 5.30 (1H, m, =CH), 5.49 (1H, m, =CH). δ_C(100.6 MHz; $CDCl_3$) 30.1, 32.3, 38.5, 52.3, 126.5, 128.8, 169.6.

Identical to literature data.[246]

Di-tert-butyl(1-Methylprop-2-enyl)malonate 271

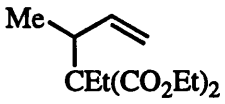


271

$C_{15}H_{26}O_4$
Exact Mass: 270.1831
Mol. Wt.: 270.3680
C, 66.64; H, 9.69; O, 23.67

Title compound was obtained as a colourless oil. R_f 0.32 (5% Et_2O/ light petroleum); (Found: C, 66.4; H, 9.66. $C_{25}H_{20}O_3$ requires C, 66.64; H, 9.69%); ν_{max}/cm^{-1} 1730 (C=O); δ_H(400 MHz; $CDCl_3$) 1.09 (3H, d, *J* 6.6, Me), 1.44 (9H, s, C(CH_3)), 1.46 (9H, s, C(CH_3)), 2.82-2.88 (1H, m, C*H*CH=CH_2), 3.05 (1H, d, *J* 8.6, C*H*(CO_2^{t}Bu)$_2$), 4.99 (1H, dd, *J* 1.0, 10.5, CH=C*H*$_2${H_A}, 5.08 (1H, dd, *J* 1.0, 17.6, CH=C*H*$_2${H_M}, 5.80 (1H, ddd, *J* 7.8, 10.5, 17.6, C*H*=CH_2); δ_C(100.6 MHz; $CDCl_3$) 18.1, 28.0, 37.7, 59.5, 81.3, 81.4, 114.7, 140.2, 167.4, 167.5; *m/z* (CI) 271 (M^+, 20%), 215 (75), 159 (100).

Diethyl (1-methylprop-2-enyl)ethylmalonate 273



273

$C_{13}H_{22}O_4$
Exact Mass: 242.1518
Mol. Wt.: 242.3144
C, 64.44; H, 9.15; O, 26.41

Title compound was obtained as a colourless oil. R_f 0.32 (8% Et_2O/ light petroleum); (Found (EI) M^+, 242.1511. $C_{13}H_{22}O_4$ requires 242.1518); (Found: C, 63.9; H, 9.03. $C_{13}H_{22}O_4$ requires C, 66.44; H, 9.15%); ν_{max}/cm^{-1}1732 (C=O); δ_H(400 MHz; $CDCl_3$) 0.85 (3H, t, *J* 7.4, CH_2CH_3), 1.08 (3H, d, *J* 6.6, Me), 1.25 (6H, t, *J* 7.4, 2x $CO_2CH_2CH_3$), 1.91 (2H, q, *J* 7.4, CH_2CH_3), 2.84 (1H, dq, *J* 6.6, $CHCH=CH_2$), 4.17 (4H, q, *J* 7.4, 2x $CO_2CH_2CH_3$), 5.03 (2H, m, $CH=CH_2$), 5.78 (1H, ddd, *J* 8.3, 10.5, 18.5, $CH=CH_2$); δ_C(100.6 MHz; $CDCl_3$) 9.4, 14.5, 17.0, 17.1, 27.5, 41.8, 61.0, 61.1, 61.6, 115.8, 115.9, 139.5, 170.9, 171.0; *m/z* (EI) 242 (M^+, 30%), 227 (45), 214 (25), 169 (100).

Diethyl (but-2-enyl)ethylmalonate 274

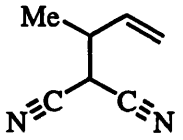
274

$C_{13}H_{22}O_4$
Exact Mass: 242.1518
Mol. Wt.: 242.3144
C, 64.44; H, 9.15; O, 26.41

Title compound was obtained as a colourless oil. R_f 0.32 (8% Et_2O/ light petroleum); (Found (EI) M^+, 242.1511. $C_{13}H_{22}O_4$ requires 242.1518); ν_{max}/cm^{-}

[1]1732 (C=O), 1222 (C-O); δ_H(400 MHz; $CDCl_3$) 0.82 (3H, t, *J* 7.3, CH_2CH_3), 1.24 (6H, t, *J* 6.9, 2x $CO_2CH_2CH_3$), 1.63 (3H, d, *J* 6.2, Me), 1.89 (2H, q, *J* 7.3, CH_2CH_3), 2.56 (2H, d, *J* 7.3, CH_2), 4.17 (4H, q, *J* 6.9, 2x $CO_2CH_2CH_3$), 5.24 (1H, dt, *J* 7.3, 15.0, CH=C*H*CH_2), 5.51 (1H, dq, *J* 6.3, 15.0, CH_3CH=CH); δ_C(100.6 MHz; $CDCl_3$) 8.4, 14.2, 18.1, 25.1, 35.1, 60.9, 124.6, 129.2, 171.2.

(1-Methyl-2-propenyl)malonitrile 291

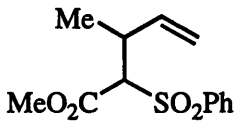


291

$C_7H_8N_2$
Exact Mass: 120.0687
Mol. Wt.: 120.1536
C, 69.97; H, 6.71; N, 23.31

Title compound was obtained as a colourless oil. R_f 0.32 (8% Et_2O/ light petroleum); (Found (EI) M^+, 120.0687. $C_7H_8N_2$ requires 120.0687); (Found: C, 70.2; H, 6.76; N, 22.1. $C_7H_8N_2$ requires C, 69.97; H, 6.71; N, 23.31); ν_{max}/cm[-1]2255 (C≡N), 1643 (C=C); δ_H(300 MHz; $CDCl_3$) 1.36 (3H, d, *J* 6.8, Me), 2.78-2.93 (1H, m, C*H*CH=CH_2), 3.69 (1H, d, *J* 5.5, $CH(CN)_2$), 5.36 (2H, dd, *J* 5.5, 15.8, CH=CH_2), 5.81 (1H, ddd, *J* 7.5, 10.2, 15.8, C*H*=CH_2); δ_C(75.4 MHz; $CDCl_3$) 17.0, 29.4, 39.4, 111.7, 111.8, 119.7, 135.2; *m/z* (EI) 120 (M^+, 30%), 105 (20), 55 (100).

(1-methyl-2-propenyl)phenylsulfonylacetate 293



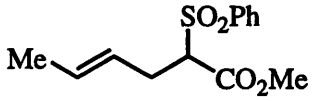
293

$C_{13}H_{16}O_4S$
Exact Mass: 268.0769
Mol. Wt.: 268.3270
C, 58.19; H, 6.01; O, 23.85; S, 11.95

The general procedure (**1**) for palladium catalysed allylic substitution was followed and the reaction was heated at reflux to give the crude product, which was purified by silica gel column chromatography using (40% Et_2O/light petroleum) to give the title compound as a colourless oil. R_f 0.23 (40% Et_2O/light petroleum); (Found (FAB^+) MH^+, 269.0840. $C_{13}H_{16}O_4S$ requires MH^+, 269.0847); ν_{max}/cm^{-1}1738 (C=O), 1324 (S=O), 1235 (C-O), 1148(S=O); δ_H(300 MHz; $CDCl_3$) 1.11 and 1.36 (3H, d, *J* 6.8, Me), 2.98-3.12 (1H, m, C*H*Me), 3.47 and 3.62 (3H, s, CO_2Me), 3.92 and 3.97 (1H, two d, *J* 9.0, 8.6, C*H*(CO_2Me)(SO_2Ph), 5.0-5.15 (2H, m, CH=CH_2), 5.63-5.89 (1H, m, C*H*=CH_2), 7.52-7.61 (2H, m, Ar), 7.64-7.70 (1H, m, Ar), 7.86-7.93 (2H, m, Ar); δ_C(75.4 MHz; $CDCl_3$) 18.3, 18.7, 37.5, 37.9, 52.8, 53.2, 75.6, 76.1, 116.7, 117.1, 129.1, 129.2, 129.4, 129.6, 134.4, 134.5, 138.2, 138.3, 138.8, 166.1.

Identical to literature data.[244]

(But-2-enyl)phenylsulfonylacetate 294



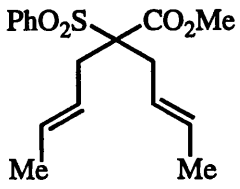
294

$C_{13}H_{16}O_4S$
Exact Mass: 268.0769
Mol. Wt.: 268.3270
C, 58.19; H, 6.01; O, 23.85; S, 11.95

Title compound was obtained as a colourless oil. R_f 0.23 (40% Et_2O/ light petroleum); (Found (FAB$^+$) MH^+, 269.0840. $C_{13}H_{16}O_4S$ requires MH^+, 269.0847); ν_{max}/cm^{-1} 1738 (C=O), 1324 (S=O), 1235 (C-O), 1148(S=O); $^{\delta}H$ (300 MHz, $CDCl_3$) 1.61 (3H, dd, *J* 1.2, 6.5, Me), 2.56-2.74 (2H, m, CH_2), 3.65 (3H, s, CO_2Me), 4.01 and 4.04 (1H, two d, *J* 3.9, 3.9, C*H*(CO_2Me)(SO_2Ph), 5.20-5.30 (1H, m, CH=CH), 5.49-5.58 (1H, m, CH=CH), 7.52-7.61 (2H, m, Ar), 7.64-7.70 (1H, m, Ar), 7.86-7.93 (2H, m, Ar).

Identical to literature data.[243]

2-Benzenesulfonyl-2-but-2-enyl-hex-4-enoic acid methyl ester 295



295

$C_{17}H_{22}O_4S$
Exact Mass: 322.1239
Mol. Wt.: 322.4184
C, 63.33; H, 6.88; O, 19.85; S, 9.94

Title compound was obtained as a colourless oil. This compound was isolated in small amounts from the reaction of methyl phenylsulfonylacetate and but-2-enyl acetate. R_f 0.65 (40% Et_2O/light petroleum); (Found (FAB^+) M^+, 322.1230. $C_{13}H_{16}O_4S$ requires M^+, 322.1230); ν_{max}/cm^{-1}1732 (C=O), 1307 (S=O), 1213 (C-O), 1147 (S=O); δ_H(400 MHz, $CDCl_3$) 1.66 (6H, dd, *J* 1.2, 6.6, 2x Me), 2.71-2.84 (4H, m, 2x CH_2), 3.64 (3H, s, CO_2Me), 5.37-5.45 (2H, m, 2x CH=CH), 5.51-5.59 (2H, m, 2x CH=CH), 7.52-7.57 (2H, m, Ar), 7.64-7.68 (1H, m, Ar), 7.80-7.87 (2H, m, Ar); δ_C(75.4 MHz; $CDCl_3$) 18.5, 34.1, 53.1, 128.8, 128.9, 130.4, 130.9, 131.3, 134.2, 136.8, 168.2; *m/z* (FAB^+) 323 (MH^+, 100%), 181 (30), 143 (10).

General procedure (6) for the palladium catalysed allylic substitution of isocinnamyl acetate with soft carbon nucleophiles in the presence of monophosphine ligands.

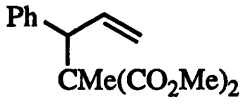
Into an evacuated round-bottomed flask containing a stirring bead, were placed $[(C_3H_5)PdCl]_2$ (0.021 g, 0.0567 mmol, 2.5 mol%) and Cy_3P (0.063 g, 0.227 mmol, 10 mol%). The flask was flushed with nitrogen and dry THF (2 mL) was added. The pale yellow solution was stirred for 10-15 min, before the addition of isocinnamyl acetate (0.4 g, 2.27 mmol, 1 equiv.). This solution was then added into a solution of the nucleophile generated *in situ* from the appropriate malonate (3.40 mmol, 1.5 equiv.) and NaH (0.136 g, 3.40 mmol, 60% w/w in mineral oil, 1.1 equiv. to malonate), in THF (20 mL). The reaction mixture was stirred at room temperature until no more starting material was observed by GC. The reaction mixture was quenched by passing it through a small pad of silica. (Any sample of the reaction mixture analysed by GC was also subjected to this treatment.) The

ratio of branched to linear products was determined by ^{1}H NMR. The products were purified by silica gel column chromatography.

General procedure (7) for the palladium catalysed allylic substitution of cinnamyl acetate with soft carbon nucleophiles in the presence of monophosphine ligands.

Into an evacuated round-bottomed flask containing a stirring bead, were placed $[(C_3H_5)PdCl]_2$ (0.021 g, 0.0567 mmol, 2.5 mol%) and Cy_3P (0.063 g, 0.227 mmol, 10 mol%). The flask was flushed with nitrogen and dry THF (2 mL) was added. The pale yellow solution was stirred for 10-15 min, before the addition of cinnamyl acetate (0.4 g, 2.27 mmol, 1 equiv.). This solution was then added into a solution of the nucleophile generated *in situ* from the appropriate malonate (3.40 mmol, 1.5 equiv.) and NaH (0.136 g, 3.40 mmol, 60% w/w in mineral oil, 1.1 equiv. to malonate), in THF (20 mL). The reaction mixture was stirred at room temperature until no more starting material was observed by GC. The reaction mixture was quenched by passing it through a small pad of silica. (Any sample of the reaction mixture analysed by GC was also subjected to this treatment.) The ratio of branched to linear products was determined by ^{1}H NMR. The products were purified by silica gel column chromatography.

Dimethyl(1-phenyl-2-propenyl)metylmalonate 278



278

$C_{15}H_{18}O_4$
Exact Mass: 262.1205
Mol. Wt.: 262.3048
C, 68.69; H, 6.92; O, 24.40

The general procedure (**6**) for palladium catalysed allylic substitution was followed to give the crude product, which was purified by silica gel column chromatography using (light petroleum/ EtOAc 6:1) to give the title compound as a colourless oil. R_f 0.61 (light petroleum/ EtOAc 6:1); ν_{max}/cm^{-1} 3000, 2952, 1732, 1494, 1454, 1434, 1380, 1246, 1111, 993, 992, 753, 704; δ_H(300 MHz; $CDCl_3$) 1.43 (3H, s,), 3.62 (3H, s), 4.10 (1H, d, *J* 8.6), 5.11 (1H, d, *J* 16.8), 5.12 (1H, d, *J* 10.0), 6.32 (1H, ddd, *J* 8.6, 10.0, 16.8), 7.18-7.34 (5H, m); δ_C(75.4 MHz; $CDCl_3$) 52.3, 54.5, 58.8, 117.9, 127.2, 128.3, 129.6, 137.0, 139.1, 171.4, 171.6. Identical to literature data.[242]

Dimethyl (3-Phenyl-2-propenyl)methylmalonate 279

279

$C_{15}H_{18}O_4$
Exact Mass: 262.1205
Mol. Wt.: 262.3048
C, 68.69; H, 6.92; O, 24.40

The general procedure (**7**) for palladium catalysed allylic substitution was followed to give the crude product, which was purified by silica gel column

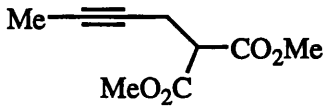
chromatography using (light petroleum/ EtOAc 6:1) to give the title compound as a colourless oil. R_f 0.61 (light petroleum/ EtOAc 6:1); ν_{max}/cm^{-1} 3032, 3002, 2956, 1728; δ_H(300 MHz; $CDCl_3$) 1.45 (3H, s,), 2.77 (2H, dd, *J* 7.5, 1.4,), 3.73 (6H, s,), 6.08 (1H, dt, *J* 15.8, 7.3,), 6.45 (1H, d, *J* 15.7,), 7.20-7.35 (5H, m, Ar). δ_C(75.4 MHz; $CDCl_3$) 19.7, 39.4, 52.3, 54.0, 124.0, 125.9, 127.2, 128.2, 134.0, 137.3, 172.3.

Identical to literature data.[242]

General procedure for the nucleophilic substitution of 1-bromo-2-butyne with malonates.

Into an evacuated round-bottomed flask was placed 1-bromo-2-butyne (0.52 mL, 0.8g, 6 mmol, 1 equiv.) and dry THF (20 mL). The resulting solution was cooled to –78 °C. To this solution was slowly added the malonate nucleophile generated *in situ* from the appropriate malonate (9 mmol, 1.5 equiv.) and NaH (0.40 g, 60% w/w in mineral oil, 9.9 mmol, 1.1 equiv. to malonate) in THF (25 mL). After stirring for 15 min. the reaction was gradually warmed up to room temperature and stirring was continued for a further 20 h. The reaction was then quenched with addition of sat. ammonium chloride. It was extracted with DCM. The organic layer was washed with ammonium chloride x 2 and water. The organic phase was then dried over $NaSO_4$, filtered and evaporated to give the crude product.

Dimethyl(but-2-ynyl)malonate 285

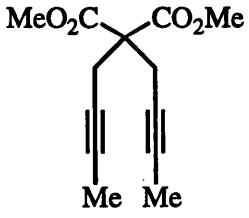


$C_9H_{12}O_4$
Exact Mass: 184.0735
Mol. Wt.: 184.1914
C, 58.69; H, 6.57; O, 34.75

The general procedure for nucleophilic substitution of 1-bromo-2-butyne was followed to give the crude product, which was purified by silica gel column chromatography using (15% Et_2O/ light petroleum) to give the title compound as a colourless oil (36%); R_f 0.48 (30% Et_2O/ light petroleum). (Found (FAB^+) MH^+, 185.0803. $C_9H_{13}O_4$ requires 185.0813); δ_H(270 MHz; $CDCl_3$) 1.75 (3H, dd, *J* 2.6, 2.6, Me), 2.73 (2H, dq, *J* 2.6, 7.7, CH_2), 3.55 (1H, t, *J* 7.7, CH), 3.76 (3H, s, CO_2Me), 3.77 (3H, s, CO_2Me); δ_C(100.5 MHz, $CDCl_3$) 3.6, 19.0, 51.5, 52.7, 74.5, 77.9, 168.4; *m/z* (FAB^+) 185 (MH^+, 100%), 111 (10), 97 (20), 82 (8), 56 (5).

Identical to literature data.[248]

2,2-Di-but-2-ynyl-malonic acid dimethyl ester 288

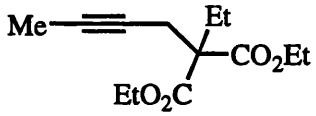


$C_{13}H_{16}O_4$
Exact Mass: 236.1048
Mol. Wt.: 236.2670
C, 66.09; H, 6.83; O, 27.09

purified by silica gel column chromatography using (15% Et_2O/ light petroleum) to give the title compound as a colourless solid (14%). R_f 0.58 (30% Et_2O/ light petroleum); (Found (FAB^+) MH^+, 237.1123. $C_{13}H_{17}O_4$ requires 237.1126); δ_H(270 MHz; $CDCl_3$) 1.75 (6H, dd, *J* 2.4, 2.6, 2x Me), 2.90 (4H, dq, *J* 2.4, 2x CH_2), 3.74 (6H, s, $C(CO_2Me)_2$; δ_C(67.9 MHz, $CDCl_3$) 3.5, 22.9, 29.6, 52.8, 57.0, 73.1, 78.9, 169.7; *m/z* (FAB^+) 237 (MH^+, 100%), 205 (10), 117 (10), 97 (10).

Identical to literature data.[249]

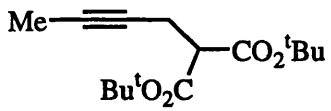
Diethyl (but-2-ynyl)ethylmalonate 287



$C_{13}H_{20}O_4$
Exact Mass: 240.1361
Mol. Wt.: 240.2986
C, 64.98; H, 8.39; O, 26.63

The general procedure for nucleophilic substitution of 1-bromo-2-butyne was followed to give the crude product, which was purified by silica gel column chromatography using (8% Et_2O/ light petroleum) to give the title compound as a colourless oil (98%). R_f 0.38 (10% Et_2O/ light petroleum); (Found (FAB^+) M^+, 241.1434. $C_{13}H_{20}O_4$ requires 241.1439); ν_{max}/cm^{-1} 2236 (C≡C), 1733 (C=O); δ_H (400 MHz; $CDCl_3$) 0.81 (3H, t, *J* 7.4, CH_2CH_3), 1.23 (6H, t, *J* 7.03, 2x $CO_2CH_2CH_3$), 1.72 (3H, t, *J* 2.7, Me), 2.05 (2H, q, *J* 7.4, CH_2CH_3), 2.72 (2H, q, *J* 2.7, CH_2), 4.17 (4H, q, *J* 7.03, 2x $CO_2CH_2CH_3$); δ_C(100.6 MHz, $CDCl_3$) 3.9, 8.8, 14.5, 22.8, 25.3, 57.9, 61.6, 73.8, 78.7, 170.7; *m/z* (FAB^+) 241 (MH^+, 100%).

Di-tert-butyl (but-2-ynyl)malonate 286

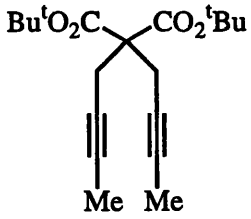


$C_{15}H_{24}O_4$
Exact Mass: 268.1674
Mol. Wt.: 268.3522
C, 67.14; H, 9.01; O, 23.85

The general procedure for nucleophilic substitution of 1-bromo-2-butyne was followed to give the crude product, which was purified by silica gel column chromatography using (5% Et_2O/ light petroleum) to give the title compound as a colourless oil (98%). R_f 0.30 (5% Et_2O/ light petroleum); (Found (FAB^+) MH^+, 269.1749. $C_{15}H_{25}O_4$ requires 269.1749); ν_{max}/cm^{-1}1730 (C=O); δ_H(400 MHz; $CDCl_3$) 1.47 (18H, s, 2x $C(CH_3)_3$), 1.75 (3H, s, Me), 2.61 (2H, m, CH_2), 3.30 (1H, t, *J* 7.8, $CH(CO_2{}^tBu)_2$. δ_C(100.6 MHz; $CDCl_3$) 15.2, 24.4, 49.9, 71.5, 78.1, 163.9; *m/z* (FAB^+) 269 (MH^+, 100%), 213 (55), 157 (70).

Identical to literature data.[250]

2,2-di-but-2-ynyl-malonic acid di-*tert*-butyl ester 289



$C_{19}H_{28}O_4$
Exact Mass: 320.1987
Mol. Wt.: 320.4278
C, 71.22; H, 8.81; O, 19.97

The general procedure for nucleophilic substitution of 1-bromo-2-butyne was followed to give the crude product, which was purified by silica gel column

chromatography using (5% Et_2O/ light petroleum) to give the title compound as a colourless oil (8%); (Found (FAB^+) MH^+, 321.2065. $C_{19}H_{29}O_4$ requires 321.2065); R_f 0.38 (5% Et_2O/ light petroleum); δ_H(400 MHz; $CDCl_3$) 1.45 (18H, s, 2x $C(CH_3)_3$), 1.75 (6H, t, *J* 2.3, 2x CH3), 2.78 (4H. q, *J* 2.3, 2x CH_2); δ_C (100.6 MHz; $CDCl_3$) 23.1, 28.2, 58.1, 74.1, 78.2, 81.8, 168.6; *m/z* (FAB^+) 321 (MH^+, 35%), 265 (40), 209 (100), 57 (85).

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